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REACTION TO THE PRESUMPTIVE KAHN TEST IN PATIENTS WITH *BEJEL* (NON-VENEREAL SYPHILIS)

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Patients presenting themselves at the clinic in Deir-ez-Zor fall into three distinct and mutually exclusive social groups: (*a*) the Christians, numerically a small group; (*b*) the townspeople, and (*c*) the seminomad Bedouin villagers of the region of the Euphrates.[1]

Syphilis is seen in the clinic in two forms: (*a*) the venereal type, known as *franghi*, and (*b*) the nonvenereal type, known as *bejel*.[2] The venereal type is seen in the Christians and in some of the townspeople. The nonvenereal type is seen in the townspeople and the Bedouins.

Using the standard Kahn test as our criterion, my associates and I have found syphilis in 15.2 per cent of the Christians, 26.5 per cent of the townspeople and 58.7 per cent of the Bedouins.[3]

We have noted, however, that many of the townspeople and Bedouins who stated that they had had *bejel* in childhood had negative reactions to the standard Kahn test. In the Bedouin community, for example, more than 75 per cent of the adults said that they had had *bejel*, mostly in childhood, but the percentage of positive reactions to the standard Kahn test was from 10 to 15 per cent less.[2] Are the histories incorrect, or is the standard Kahn test not sensitive enough to detect the presence of the untreated latent disease in all cases?

One cannot reject the evidence of the histories. Experience has shown that the Bedouins are accurate in their anamneses concerning *bejel*.[2] Most adults know definitely whether or not they have had *bejel* and, if so, at what age. Each parent knows which of his children has had *bejel*.

Further, *bejel* is not confused with other diseases. The Bedouins do not have a common name for tuberculosis, infestation with hookworm or amebiasis, though many suffer from these diseases, but they know the "*bejel* picture" and distinguish the eruption in this disease from those of smallpox and measles.

1. Hudson, E. H.: Internat. Rev. Missions **19**:428, 1930.

2. Hudson, E. H.: Arch. Dermat. & Syph., to be published.

3. (*a*) Hudson, E. H.: Am. J. Syph. **16**:447, 1932; **17**:10, 1933. (*b*) Hudson, E. H., and Young, A. L.: J. Christian M. A. India **8**:284, 1933.

Lastly, there are frequently objective signs, such as exostoses, cutaneous scars, saddle nose and pharyngeal cicatrices, which give indubitable support to the patient's statement, even in the presence of a negative reaction to the standard Kahn test.

We have assumed in the past that the discrepancy between the percentage of histories of *bejel* and the percentage of positive Kahn reactions was due to quantitative diminution in the circulating reagin below the threshold of the standard reaction in a proportion of cases. If this assumption is correct, a more sensitive test should give 10 or 15 per cent more positive readings in a given series of Bedouins than the standard test.

The presumptive Kahn test is so called because it is carried out with a "sensitized" antigen. In some cases this oversensitiveness leads to false positive readings. On the other hand, it is of recognized usefulness in the detection of syphilis in which there are negative serologic reactions to other tests.[4] This feature of the test made it seem

TABLE 1.—*Distribution According to Sex of 290 Patients Subjected to the Presumptive Kahn Test*

	Christians	Townspeople	Bedouins	Total
Males	39	48	57	144
Females	45	69	32	146
Total	84	117	89	290

especially applicable to the group of our patients who had a history of syphilis in childhood but who showed a negative reaction to the standard Kahn test. Our feeling that the standard Kahn test was failing to detect many undoubted cases of syphilis led us to project a trial of the presumptive antigen on a series of serums.

MATERIAL

Between Jan. 25 and June 19, 1933, 290 persons were subjected to the presumptive Kahn test of the blood. These were patients admitted to the general clinic, clinically both syphilitic and nonsyphilitic, and comprised all those who during the period of five months had given a negative reaction to the standard Kahn test, which we were carrying out at that time on practically all the patients admitted. A few patients with a doubtful or positive reaction to the standard Kahn test were included as controls.

Table 1 shows that the group was almost equally divided between males and females and that there were 84 Christians, 117 townspeople and 89 Bedouins.

4. The Standard and the Presumptive Kahn Reactions, editorial, J. A. M. A. **96**:530, 1931.

Table 2 divides the 290 patients into age groups; it will be noted that they are well distributed, with a preponderance in the age groups from 20 to 40.

The reaction to the standard Kahn test of the blood was negative in 257 cases, doubtful (±) in 15 and positive in 18. Thus this reaction failed to indicate or even to suggest the presence of syphilis except in 33 (11.4 per cent) of the group of 290 persons.

TABLE 2.—*Distribution According to Age of 290 Patients Subjected to the Presumptive Kahn Test*

Age, Years	Christians	Townspeople	Bedouins	Total
1–9	2	7	3	12
10–19	9	11	6	26
20–29	33	39	23	95
30–39	20	32	24	76
40–49	10	17	12	39
50–59	9	6	11	26
60–69	1	5	5	11
70 and over	0	0	5	5
Total	84	117	89	290

TABLE 3.—*Social Groups Compared as to History, Reaction to the Standard Kahn Test and Reaction to the Presumptive Kahn Test*

	History of Syphilis				Reaction to Standard Kahn Test			Reaction to Presumptive Kahn Test			
								Negative		Positive	
	Blank	No	Doubtful	Yes	Negative	Doubtful	Positive	Number	Percentage	Number	Percentage
Christians (84 cases)	30	50	1	3	73	4	7	61	72.6	23	27.4
	95.2%		4.8%		86.9%	13.1%					
Townspeople (117 cases)	20	56	5	36	109	4	4	63	53.8	54	46.2
	64.9%		35.1%		93.2%	6.8%					
Bedouins (89 cases)	4	32	0	53	75	7	7	36	40.4	53	59.6
	40.4%		59.6%		84.3%	15.7%					
Total (290 cases)	54	138	6	92	257	15	18	160	55.1	130	44.9
	66.2%		33.8%		88.6%	11.4%					

On the other hand, the presumptive precipitation test revealed 130 (44.9 per cent) positive reactions. Doubtful and weakly positive reactions to the presumptive Kahn test were regarded as negative. Only those reactions to the presumptive Kahn test which would rank as 2+ or more were reported positive. In the following paragraphs this result is analyzed in relation to the three social groups.

Christians.—Sixty-one (72.6 per cent) of the 84 Christians had a negative reaction to the presumptive Kahn test, and 23 (27.4 per cent) had a positive reaction (table 3). Fifty-nine of the 61 who showed a negative reaction also had

a negative reaction to the standard Kahn test and either no history of syphilitic infection (38) or a blank history (21). The 2 remaining patients with a negative reaction to the presumptive Kahn test had a negative reaction to the standard Kahn test but a history of syphilis.

Twelve of the 23 who showed a positive reaction to the presumptive Kahn test had a negative reaction to the standard Kahn test and either no history of syphilitic infection (8) or a blank history (4). Four of the 23 who had a positive reaction to the presumptive Kahn test had a doubtful reaction to the standard Kahn test with either no history of syphilitic infection (3) or a blank history (1). In the remaining 7 cases the positive reaction to the presumptive Kahn test was supported by a history of syphilitic infection in 2 cases and by a positive reaction to the standard Kahn test in all 7.

Thus, among the 23 (27.4 per cent) Christians who had a positive reaction to the presumptive Kahn test there was poor support for a diagnosis of syphilis in the history (4.8 per cent) and in the reaction to the standard Kahn test (13.1 per cent). Two factors in this group partially account for this. In the first place, since syphilis among the Christians is a venereal disease the patient does not readily admit having had it, and this factor undoubtedly reduces the percentage of histories of syphilitic infection. In the second place, the Christians are adults when they acquire the infection; they recognize the desirability of treatment, are able to pay for it and often carry through a course in the care of a physician. Thus the factor of treatment reduces the likelihood of positive reactions among them.

The reaction to the presumptive Kahn test might thus appear positive in treated persons who have a history of syphilitic infection and whose reactions to the standard Kahn test were negative. It was in this group, as will be seen, that false positive reactions to the presumptive Kahn test were proportionally most numerous—that is, there was the greatest incompatibility between the reactions to the presumptive Kahn test and the clinical diagnoses.

In table 4 the final clinical diagnosis for the cases in each group is given in relation to the history and the reaction to the blood tests. The decision as to the final diagnosis in each case was made from the patient's record, the following factors being taken into consideration: (*a*) The history. Was it definite in date, circumstantial in detail and vouched for by other members of the family, and had treatment been received in the form of either inhalations of mercury in Arab fashion or injections made by a physician? (*b*) The results of physical examination. Were there obvious signs of syphilis, past or present, especially in the nose, throat, skin and bones? (*c*) The reaction to the blood tests, both the standard Kahn test and the presumptive Kahn test. (*d*) The effect of our treatment. Were ulcers healed and pains in the bones relieved with bismuth?

It will be seen (table 4) that among the Christians 10 of the 23 persons who had shown a positive reaction to the presumptive Kahn test were pronounced free from syphilis, and for 4 the diagnosis was doubtful. In other words, for 10 the diagnosis based on the serologic test was shown clinically to be falsely positive, and in 4 the condition was doubtfully syphilitic, leaving only 9 cases in which the condition was certainly syphilitic, 2 more than the standard Kahn test showed.

All the 7 Christians with a positive reaction to the standard Kahn test were clinically syphilitic. The 4 with a doubtful reaction to the standard Kahn test were all doubtfully syphilitic. The Christian with an uncertain history was undoubtedly syphilitic, and of the 3 with a positive history, 2 were surely syphilitic and 1 was possibly syphilitic.

Townspeople.—Sixty-three (53.8 per cent) of the 117 townspeople had a negative reaction to the presumptive Kahn test, and 54 (46.2 per cent) had a positive reaction (table 3). Fifty-three of the 63 with a negative reaction also had a negative reaction to the standard Kahn test and either no history of syphilitic infection (40) or a blank history (13). All the 10 remaining persons with a negative reaction to the presumptive Kahn test had a negative reaction to the standard Kahn test, but all had a history of syphilitic infection.

Twenty-one of the 54 with a positive reaction to the presumptive Kahn test had a negative reaction to the standard Kahn test and either no history of syphilitic infection (14) or a blank history (7). In a further series of 6 cases 1 person had a doubtful reaction to the standard Kahn test and 5 had a doubtful history.

TABLE 4.—*Final Clinical Diagnoses Compared with Histories and Results of Tests of Blood*

	Number of Cases	Final Clinical Diagnosis					
		No Syphilitic Infection		Uncertain		Syphilitic Infection	
		Number	Percentage	Number	Percentage	Number	Percentage
Reactions to Presumptive Kahn Test							
Positive	130						
Christians	23	10	43.5	4	17.4	9	39.1
Townspeople	54	11	20.4	16	29.6	27	50.0
Bedouins	53	0	....	6	11.3	47	88.7
Reactions to Standard Kahn Test							
Positive	18						
Christians	7	0	....	0	....	7	100.0
Townspeople	4	0	....	0	....	4	100.0
Bedouins	7	0	....	0	....	7	100.0
Doubtful reactions	15						
Christians	4	0	....	4	100.0	0	....
Townspeople	4	0	....	1	25.0	3	75.0
Bedouins	7	0	....	0	....	7	100.0
History							
Definite	92						
Christians	3	0	....	1	33.0	2	67.0
Townspeople	36	0	....	10	27.8	26	72.2
Bedouins	53	0	....	15	28.3	38	71.7
Uncertain	6						
Christians	1	0	....	0	....	1	100.0
Townspeople	5	2	40.0	2	40.0	1	20.0
Bedouins	0	0	....	0	....	0	....

Of the remaining 27 persons who had a positive reaction to the presumptive Kahn test, 20 gave a history of syphilitic infection but did not have a positive reaction to the standard Kahn test; there was a positive reaction to the standard Kahn test but no history of syphilitic infection in 1, and in 6 both the history and the reaction to the standard Kahn test (in 3 positive and in 3 doubtful) suggested syphilitic infection.

Thus, among the 54 (46.2 per cent) townspeople who had a positive reaction to the presumptive Kahn test there was good support for a diagnosis of syphilis in the history (35.1 per cent) but poor support in the reaction to the standard Kahn test (6.8 per cent).

The latter is perhaps an unexpected finding, but the explanation appears in the fact that 34 of the 36 patients with a history of syphilitic infection had this condi-

tion in childhood and only 2 in adult life. At least 34 of the 36, therefore, had nonvenereal syphilis (*bejel*) and whether treated or not might give a negative reaction when tested by the standard Kahn test, as they were, years later. On the other hand, the latency of the disease in some cases did not escape detection by the presumptive Kahn test. The percentage of positive reactions to this test therefore rises in proportion to the history and is far above the percentage of positive reactions to the standard Kahn test.

It will be seen (table 4) that among the townspeople 11 of the 54 persons with a positive reaction to the presumptive Kahn test were pronounced free from syphilis, and for 16 the diagnosis was doubtful. In other words, in this group 11 persons were shown clinically to have given a false positive reaction and 16 were doubtfully syphilitic, leaving 27 certainly syphilitic, 23 more than the standard Kahn test showed.

All the 4 persons with a positive reaction to the standard Kahn test were clinically syphilitic. Of the 4 who had a doubtful reaction to the standard Kahn test, 3 were certainly syphilitic and 1 was possibly syphilitic. Of the 36 with a history of syphilitic infection, 26 were clinically syphilitic, and for 10 the reaction was uncertain. Of the 5 with an uncertain history, 2 gave a negative reaction; 2 gave an uncertain reaction, and 1 was certainly syphilitic.

Bedouins.—Thirty-six (40.4 per cent) of the 89 Bedouins had a negative reaction to the presumptive Kahn test, and 53 (59.6 per cent) had a positive reaction (table 3). Twenty of the 36 with a negative reaction also had a negative reaction to the standard Kahn test and either no history of syphilitic infection (19) or a blank history (1). A further series of 15 persons who had a negative reaction to the presumptive Kahn test had a negative reaction to the standard Kahn test but a history of syphilitic infection. The remaining patient had a history of syphilitic infection and a doubtful reaction to the standard Kahn test.

Sixteen of the 53 persons who showed a positive reaction to the presumptive Kahn test gave a negative (14 cases) or doubtful (2 cases) reaction to the standard Kahn test and had either no history of syphilitic infection (13 cases) or a blank history (3 cases). Of the remaining 37 patients, 26 had a history of syphilitic infection but gave a negative reaction, and in the case of 11 both the history and the reaction to the standard Kahn test (in 4 doubtful and in 7 positive) suggested syphilitic infection.

Thus, among the 53 (59.6 per cent) Bedouins who had a positive reaction to the presumptive Kahn test there was good support for the diagnosis of syphilis in the history (59.6 per cent), but—as in the case of the townspeople and for the same reason—less support in the reaction to the standard Kahn test (15.7 per cent).

Here again the scarcity of positive reactions to the standard Kahn test is obviously due to the latency of the disease. In 51 of the 53 persons who gave a history of syphilitic infection the condition was said to be infection with *bejel* in childhood, leaving only 2 cases in which the disease might possibly be of venereal origin. Even in these 2 cases it was probably also of nonvenereal origin.

Thus, in table 4 one finds the contrast between the Christians and the townspeople carried still further in the Bedouins, among whom 47 of 53 with a positive reaction to the presumptive Kahn test were clinically syphilitic and for the remaining 6 the diagnosis was uncertain. None showed a negative reaction. In this group there were no false positive reactions among the reactions to the presumptive Kahn test, and there were 46 more positive reactions than the standard Kahn test showed.

Also, all the 7 persons with a positive reaction to the standard Kahn test and all the 7 with a doubtful reaction to this test were certainly syphilitic. Of the 53 with a history of syphilitic infection, 15 were uncertainly, and 38 certainly, syphilitic. None was certainly nonsyphilitic.

SPECIFICITY OF THE KAHN REACTIONS IN THE PRESENT SERIES

The committee of five which has recently reported an evaluation of serodiagnostic tests for syphilis [5] listed seven diseases or conditions which might affect the specificity of the reactions to these tests. We found none of these diseases or conditions in our patients in a degree large enough to affect our percentage figures for the reaction to either the standard or the presumptive Kahn test.

There were no cases of leprosy, malignant neoplastic disease, jaundice or high fever in our series. Instances of pregnancy were not numerous.

As to malaria, it is not endemic in the region of Deir-ez-Zor.[6] Most of the patients with malaria admitted to the clinic are Christians who have come to Deir-ez-Zor from regions of endemic malaria. Among 123 consecutive Christian patients (seen from January to June 1933) there were 14 in whom malaria could not be definitely excluded. Among 193 consecutive townspeople seen during the same period there were possibly 4 cases of malaria, and among 281 consecutive Bedouin patients there was none.

Among the 123 Christians there were 2 cases of pulmonary tuberculosis; among the 193 townspeople there were 10 cases of pulmonary tuberculosis and 1 case of osseous tuberculosis; among the 281 Bedouins there were 8 cases of pulmonary tuberculosis, 1 of glandular tuberculosis and 3 of osseous tuberculosis.

It may therefore be assumed that no adjustment of our percentages needs to be made to rule out the possible presence of positive reactions due to conditions other than syphilis.

COMPARATIVE SENSITIVENESS OF THE STANDARD AND PRESUMPTIVE KAHN TESTS

Most of the presumptive Kahn tests were done on serums which showed a negative reaction by the standard Kahn test. In those cases, however, in which the reaction to the standard Kahn test was positive the reaction to the presumptive Kahn test was also positive, and in all but 1 of the cases in which there was a doubtful positive reaction to the standard Kahn test there was a positive reaction to the presumptive

5. Cumming, H. S.; Hazen, H. H.; Sanford, H. H.; Senear, F. E.; Simpson, W. M., and Vonderlehr, R. A.: J. A. M. A. **104**:2083, 1935.

6. Hudson, E. H.: Bruxelles-méd. **12**:763, 1932.

Kahn test. It may therefore be assumed that in practically all the cases in which there was a positive or doubtful reaction to the standard Kahn test the reaction to the presumptive Kahn test, if it had been done, would have been positive. An analysis of the results for the three social groups follows:

Of 79 consecutive serums from Christian patients, 9 gave a positive reaction and 4 gave a doubtful reaction, to the standard Kahn test. In the 4 cases in which there was a doubtful serologic reaction the clinical diagnosis was also doubtful. The 9 cases in which there was a positive serologic reaction constitute 11.4 per cent of the total. There were 11 more cases in which there was a positive reaction to the presumptive Kahn test, but in 10 of these there were no clinical signs of syphilitic infection. The presumptive Kahn test, therefore, elicited a total of 10 positive reactions, or 12.7 per cent of the total number, an increase of sensitiveness of 1.3 per cent among the Christians.

Of 132 consecutive serums from townspeople, 38 gave positive reactions and 3 gave doubtful reactions to the standard Kahn test, but the persons who showed the doubtful reactions were clinically syphilitic. One may therefore count 41 (31.1 per cent) positive reactions to the standard Kahn test. There were 39 more positive reactions to the presumptive Kahn test, but 20 of these persons showed no clinical signs or showed uncertain signs. The presumptive Kahn test, therefore, elicited a total of 60 positive reactions, or 45.5 per cent, an increase of sensitiveness of 14.4 per cent among the townspeople.

Of 242 consecutive serums from Bedouins, 165 gave a positive reaction and 6 gave a doubtful reaction, to the standard Kahn test. All the persons who showed a doubtful reaction were clinically syphilitic. One may therefore count 171 (70.7 per cent) positive reactions to the standard Kahn test. There were 38 other persons who showed a positive reaction to the presumptive Kahn test but in 4 of these the condition was clinically uncertain. The presumptive Kahn test, therefore, elicited a total of 205 positive reactions, or 84.7 per cent, an increase over the number of positive reactions to the standard Kahn test of 14 per cent among the Bedouins.

These figures are to be compared with those of McDermott,[7] who on the basis of 15,000 examinations found the presumptive Kahn test to be 26 per cent more sensitive for treated patients with syphilis and 2.5 per cent more sensitive for patients admitted in the routine manner to the hospital.

Our Christian group is relatively comparable to the group of patients admitted to the hospital, and the percentages of increased sensitiveness in these two groups are of the same order. The townspeople and Bedouins, with their preponderance of untreated latent infections, acquired in childhood, do not correspond to either of McDermott's groups. Their 14 per cent of increased sensitiveness in the presumptive Kahn test stands midway between the percentages shown by the patients admitted to the hospital and the treated patients.

7. McDermott, E. B.: Arch. Path. **8**:661, 1929.

SYPHILITIC MORBIDITY IN THE REGION OF THE MIDDLE EUPHRATES

In the report of our first 1,000 Kahn reactions,[3a] in which all the doubtful reactions were counted negative, 19.6 per cent of the 224 Christians, 30.4 per cent of the 530 townspeople and 55 per cent of the 242 Bedouins showed a positive reaction. In our second 1,000 Kahn reactions,[3b] in which doubtful reactions were also counted negative, 10 per cent of the 189 Christians, 21.6 per cent of the 426 townspeople and 61 per cent of the 385 Bedouins showed a positive reaction. When the reports are combined,[3b] it is found that 15.2 per cent of 413 Christians, 26.5 per cent of 956 townspeople and 58.7 per cent of 627 Bedouins gave a positive reaction.

Of 241 presumably healthy Bedouins who were not patients, 153 (63.9 per cent) had positive Kahn reactions.[3b]

The serums of 182 Bedouins were subjected to the standard Kahn test in two laboratories.[8] The Deir-ez-Zor laboratory reported 116 positive and 7 doubtful reactions, a total of 123 (67.6 per cent). It will be admitted that in these cases of latent syphilis a doubtful reaction has some diagnostic significance. The laboratory of the American University of Beirut reported 112 positive and 5 doubtful reactions, a total of 117 (64.3 per cent). The Beirut laboratory also reported 83 (45.6 per cent) positive reactions by the Kolmer-Wassermann test and 21 (11.5 per cent) anticomplementary reactions.

In 156 (85.7 per cent) of the 182 cases the clinical diagnosis of syphilis had been made. Among these 156 Bedouins the Deir-ez-Zor laboratory reported positive reactions to the standard Kahn test in 72.4 per cent, and the Beirut laboratory reported positive reactions in 71.2 per cent.

In an unselected series of 163 adult Bedouins,[8] the Dier-ez-Zor laboratory reported positive reactions to the standard Kahn test in 65 per cent.

The Beirut laboratory reported positive reactions to the standard Kahn test in 63.2 per cent; it reported positive reactions to the Kolmer-Wassermann test in 47.2 per cent and anticomplementary reactions in a further 11 per cent.

An analysis of the results obtained for the three social groups in the present study follows:

Between Jan. 25 and June 19, 1933, 123 consecutive Christian patients were admitted to the clinic. The serums of 79 were subjected to the standard Kahn test. Nine gave a positive reaction, and 4 gave a doubtful reaction. Of the 79 serums, 66 which gave doubtful or negative reactions were subjected to the presumptive Kahn test, and 11 more showed a positive reaction, making a gross total of 24 patients with a positive reaction (19.5 per cent). Of the remaining 99 patients, 55 showed no serologic or clinical signs of syphilis and 44 were not tested serologically and showed no clinical signs.

8. Hudson, E. H.: Am. J. Syph., Gonor. & Ven. Dis., to be published.

Thus the total proportion of syphilitic patients, with the Kahn tests as the sole criterion, was 19.5 per cent of the total number. This is probably too high a percentage, as table 4 indicates that in 10 (43.5 per cent) of 23 of these cases the reaction of the blood was falsely positive. The proportion of syphilitic persons among Christians should constitute about 15 per cent, which is the percentage reported in a previous series of 413 Christians.[3b] The reactions to the presumptive Kahn test do not add much, if anything, to the percentage of persons with evidence of syphilis in the Christian group.

If one takes into account the fact that all the Christians tested have been patients and that there were no nonpatient controls for this group, there is probably justification for reducing the estimate of syphilitic morbidity in the general Christian population to between 10 and 12 per cent.

In the same period of five months 193 consecutive townspeople were admitted as patients to the clinic. The serums of 132 were subjected to the standard Kahn test. Thirty-eight gave a positive reaction, and 3 gave a doubtful reaction. Of the 132 serums, 91 which gave doubtful or negative reactions were subjected to the presumptive Kahn test, and 39 more showed a positive reaction, making a gross total of 80 patients with a positive serologic reaction (41.4 per cent). Of the remainder, 52 showed no clinical or serologic signs of syphilis, and 57 were not tested serologically and showed no clinical signs. Lastly, there were 4 who were not tested but who showed positive clinical signs.

Thus, if the Kahn tests are used as the sole criterion, the number of persons with evidence of syphilis was 41.4 per cent of the total number. This may be too high a percentage, as it does not allow for false positive reactions to the presumptive Kahn test. We found that 11 (20.4 per cent) of 54 of the persons who showed a positive reaction to the presumptive Kahn test had no clinical signs of syphilitic infection.

Allowing for false positive reactions to the presumptive Kahn test and adding those cases of persons who were not tested but who had positive clinical signs, one arrives at a percentage of positively syphilitic persons among an unselected group of townspeople of about 35. This is probably correct, being about 10 per cent higher than the figure for the 956 townspeople in our previous series.[3b] The 10 per cent increase is due to the use of the presumptive Kahn test to detect cases of latent *bejel* acquired in childhood in these townspeople.

The results of tests on our nonpatient controls among the townspeople lead to the conclusion that this syphilitic morbidity is found in the general population of townspeople as well as in the more limited group of clinic patients.

In the same period of five months, 281 consecutive Bedouins were admitted as patients to the clinic. The serums of 242 were subjected to the standard Kahn test. One hundred and sixty-five gave a positive reaction, and 6 gave a doubtful reaction. Of the 242 patients, 78 who showed a doubtful or negative reaction were subjected to the presumptive Kahn test, and 38 more showed a positive reaction, making a gross total of 209 persons with a positive serologic reaction (74.4 per cent). Of the remainder, 33 showed no clinical or serologic signs, and 17 were not tested serologically and showed no clinical signs. Lastly, there were 22 who were not tested but who showed positive clinical signs; 5 of these had a definite history of syphilis, and 17 had syphilitic lesions.

Thus, if the Kahn tests are used as the sole criterion the proportion of persons with evidence of syphilis is 74.4 per cent of the total number. This is probably correct, being about the percentage of histories of syphilitic infection and 15

per cent higher than the previously reported figures for the standard reaction alone.[3b] The positive reactions to the presumptive Kahn test in cases of latent *bejel* are responsible for this rise of percentage.

One does not have to allow for false positive reactions in the case of the Bedouins, as none of the persons with a positive reaction to the presumptive Kahn test was without clinical signs (table 4). On the other hand, the 22 cases in which there were clinical signs of syphilis may be added to the total number of cases in which there were positive serologic reactions, making a final total of 231 cases of syphilitic infection (82.2 per cent) in 281 Bedouins.

When the ages of the persons with a negative reaction are analyzed, it is found that three-fourths were infants and children under 10 years of age who had "not yet" had *bejel*. If these are eliminated, the proportion of cases of syphilis in adult Bedouins rises to over 90 per cent. Our study of nonpatient controls in Bedouin subjects leads to the conclusion that this syphilitic morbidity is found in the general Bedouin population, as well as in the more limited group of Bedouin clinic patients.

Figures comparable to those just given are obtained if one approaches the question of syphilitic morbidity among the Bedouins from the standpoint of history first and only secondarily from the angle of the Kahn reaction and syphilitic lesions.

For example, of 162 presumably healthy adult Bedouin men working in archeologic excavation,[3b] 132 (81.5 per cent) said that they had had *bejel*; 18 (11.1 per cent) more had a positive reaction to the standard Kahn test, and a further series of 3 (1.8 per cent) had indubitable lesions, making a total of 153 (94.5 per cent). It is to be noted especially that these were day-laborers, presumably healthy adult men, not clinic patients.

Of 757 male and female adult Bedouins, 78.4 per cent said that they had had *bejel*, three fourths of them in childhood, and 4.8 per cent more were uncertain whether they had had *bejel*. The remaining 16.7 per cent (127 persons) stated that they had not had *bejel*, but among 90 of these who were tested 30 had a positive reaction of the blood.[3]

Thus, whether one approaches the question from the angle of serologic reactions or of a history of syphilitic infection and whether one analyzes the data for clinic patients or for presumably healthy persons, the conclusion is inescapable that in the Bedouin community as a whole, whether the members are "sick" or "well," the syphilitic morbidity in the adults is probably over 90 per cent.

The high incidence of the nonvenereal syphilis acquired in childhood known as *bejel* among the Bedouins of the region of the Euphrates presents a close parallel to the incidence of endemic yaws. A second point of striking similarity between *bejel* and yaws is the high diag-

nostic value which attaches to the patient's own statement regarding infection. It is true of *bejel*, as Saunders and Turner [9] stated of yaws in Jamaica, that a diagnosis can be made from the history alone in a large percentage of cases.

CONCLUSIONS

We have found the following percentages for the adult Bedouin population of the region of Deir-ez-Zor: Seventy-five per cent said that they had had syphilis (*bejel*).

Forty-five per cent had a positive Kolmer-Wassermann reaction and a further 11 per cent had an anticomplementary reaction.

Sixty per cent had a positive reaction to the standard Kahn test.

Seventy-five per cent had a positive reaction to the presumptive Kahn test.

Over 60 per cent of adult Bedouins said that they had had *bejel* in childhood, and most of them had never been treated. Syphilis in the adult Bedouin is therefore a latent disease.

The standard Kahn test is more sensitive than the Kolmer-Wassermann test in detecting latent syphilis, and the presumptive Kahn test is 15 per cent more sensitive than the standard Kahn test.

From a consideration of the histories, the positive reactions of the blood and the syphilitic lesions, it is permissible to conclude that over 90 per cent of adult Bedouins of the region of the Middle Euphrates are syphilitic. This percentage applies to the whole Bedouin community, the "well" and the "sick" alike.

This conclusion is adequately controlled by the figures for the Christians and the townspeople living in the same region. The syphilitic morbidity in the general adult Christian population is between 10 and 12 per cent. The morbidity among the townspeople is 35 per cent.

When syphilis, like yaws, becomes a community disease, largely acquired in childhood and largely untreated, it resembles yaws in the high diagnostic value of a history of syphilitic infection and in the high specific morbidity of the disease in the general adult population.

9. Saunders, G. M., and Turner, T. B.: South. M. J. **28**:542, 1935.

THE LIPID COMPOSITION OF THE WHITE BLOOD CELLS IN LEUKEMIA

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The bulk of present knowledge concerning the white blood cells in leukemia has been derived by the aid of the microscope. In recent years this knowledge has been supplemented by a few investigations into the chemistry and physiology of these cells. The latter field is particularly attractive: It is practically virgin soil.

Soffer and Wintrobe [1] have measured the oxygen consumption of leukocytes in vitro. They found little difference between normal and leukemic cells, but the oxygen consumption of granulocytes was greater than that of lymphocytes. This evidence suggests that the polymorphonuclear leukocyte is the more active of the two cells, and such a deduction is of interest when compared with the present findings. Glover, Daland and Schmitz [2] found that the oxygen consumption of immature forms is less than that of mature leukocytes, but this was not confirmed by Soffer and Wintrobe.[1] Glover, Daland and Schmitz [2] concluded further that glycolysis is not so marked in mature forms of the white blood cells. Preschel [3] studied leukemic lymphocytes and reported that they readily oxidize lactic acid. Leukemic leukocytes were noted by Oelkers [4] in two cases to contain the enzymes protease, erepsin, trypsin and lipase (butyrinase).

Byrom and Kay [5] noted that blood phosphorus increased with the leukocyte count in leukemia and went on to show that leukocytes contain exceptionally large amounts of phosphorus. In six cases, three of patients with leukemia and three of normal persons, they found high values for the following forms of phosphorus in the white blood cells: inorganic, total acid soluble, ester, enzyme hydrolyzable, lipoid and

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This work was begun while the author was associated with the Department of Obstetrics and Gynecology of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

1. Soffer, L. J., and Wintrobe, M. M.: J. Clin. Investigation **11**:661, 1932.
2. Glover, E. C.; Daland, G. A., and Schmitz, H. L.: Arch. Int. Med. **46**:46, 1930.
3. Preschel, E.: Klin. Wchnschr. **9**:1061, 1930.
4. Oelkers, H. A.: Arch. f. exper. Path. u. Pharmakol. **161**:344, 1931.
5. Byrom, F. B., and Kay, H. D.: Brit. J. Exper. Path. **9**:72, 1928.

residual. No marked difference was seen between normal and leukemic leukocytes. Buckman, Daland and Weld [6] also found a relation between the total amount of phosphorus in the blood and the leukocyte count which suggested that the leukocytes contain large amounts of phosphorus compounds.

The present investigation represents a continuation of studies on the lipid metabolism of the white blood cells. In previous studies my associates and I have reported the lipid content of the leukocytes in dogs,[7] in normal human adults,[8] in women during pregnancy, lactation and the puerperium,[9] in persons convalescent after operations,[10] in patients with fever and infection,[11] in patients with the leukocytosis of anesthesia [12] and in new-born infants [13] as well as in analyses on the same blood in relation to method [14] and in relation to the differential leukocyte count.[15] Work now under way includes the relation of leukocytic lipids to the opsonic index and to the blood platelets. The present report is concerned with the lipid composition of the white blood cells in chronic leukemia together with a few isolated observations in acute leukemia and Hodgkin's disease. The collection of this series of twenty cases has necessitated the cooperation of several physicians who have provided samples of blood from patients under their supervision. In particular should be mentioned D. J. Stephens, J. S. Lawrence and C. A. Elden, of Rochester, N. Y., and W. T. Connell, R. Third, G. Bird, H. Tweddell and R. Murray, of Kingston, Ontario.

PROCEDURE

From 25 to 50 cc. of blood was obtained from the subject under fasting conditions. The blood was oxalated and immediately centrifugated at full speed for from one-half to one hour to thoroughly pack the red and white cell layers. The white cells separate in the buffy layer lying between the red cells below and the plasma above. This buffy layer also contains platelets and any small particles of fibrin clot which may have formed if the blood was inadequately

6. Buckman, T. E.; Daland, G. A., and Weld, M.: Arch. Int. Med. **35**:389, 1925.

7. Boyd, E. M.: J. Biol. Chem. **91**:1, 1931.

8. Boyd, E. M.: J. Biol. Chem. **101**:623, 1933.

9. Boyd, E. M.: Surg., Gynec. & Obst. **59**:744, 1934.

10. Boyd, E. M.: Canad. M. A. J. **31**:626, 1934.

11. Boyd, E. M.: Surg., Gynec. & Obst. **60**:205, 1935.

12. Boyd, E. M.: Canad. M. A. J. **34**:159, 1936.

13. Boyd, E. M., and Wilson, K. M.: J. Clin. Investigation **14**:7, 1935.

14. Boyd, E. M.: J. Lab. & Clin. Med, to be published.

15. Boyd, E. M., and Stephens, D. J.: Proc. Soc. Exper. Biol. & Med. **33**:558, 1936.

oxalated. Blood in which clots had formed was never used. Whether or not the platelets affect the lipid composition of the buffy layer is not known but is now under investigation. In previous studies the impression was gained that the platelets do not markedly alter the lipid composition of the buffy layer. Variations in the lipid content of this layer may thus be taken to indicate for the most part changes in the lipid content of the white blood cells.

It was usually an easy matter to remove the buffy layer almost free from cells and plasma. If a larger volume of blood had been used, as employed by Willstätter and his colleagues in their brilliant studies on leukocytic enzymes of horses, the leukocytes might have been isolated entirely free from plasma and red cells. Preliminary studies[11] revealed that a relatively small contamination of plasma and erythrocytes as obtained by my method does not materially affect the true lipid values of the white blood cells. This has made it possible to make a complete analysis of the lipid composition of the leukocytes isolated from 50 cc. of blood, or less if the leukocyte count is above normal. In considering the values obtained it is probably more correct to speak of "the lipid content of the leukocyte fraction" than of "the lipid content of the leukocytes," but the difference between the two is actually negligible.

The buffy layer frequently separated as a single adhesive piece which curled up about the edges. In such instances it was readily picked off with a pair of forceps after the removal of the plasma. When the buffy layer was more fluid, it was removed bit by bit with a pair of wide forceps or with a pipet. In such instances the buffy layer with the adherent red cells and plasma was centrifugated again in a tube of small bore so that the layer of leukocytes became considerably deeper. The isolated white cells were then weighed to the nearest milligram, ground with cleaned, sharp sand and extracted with a boiling mixture of alcohol and ether. The lipid content of this extract was then determined by the Bloor oxidative micromethods as modified by me.[16] A more detailed description of the method used is to be published.[14]

GROUPS STUDIED

The present series includes nine patients with chronic myelogenous leukemia, eight with chronic lymphatic leukemia, one with acute myeloid leukemia, two with Hodgkin's disease and thirty normal adults. A report of the lipid composition of the white blood cells in eight normal young women was included in the original contribution on method.[8] A larger series of normal subjects was obviously desirable. To seven of the eight normal persons previously studied have been added twenty-three more, making thirty in all. The values found for the lipids in the leukocytes of one of the eight normal persons previously studied have been excluded on the basis of probable error as being too high. The subject was a young woman who had had a minor operation some time previously but whose leukocytes were hematologically normal and who appeared in perfect health. It was subsequently shown[10] that even a minor operation may be followed by a considerable increase in the lipid of the white blood cells.

16. (*a*) Boyd, E. M.: J. Biol. Chem. **101**:323, 1933; (*b*) **10**:61, 1935. (*c*) Boyd.[7]

RESULTS

Total Lipid in Blood Leukocytes in Chronic Leukemia.—The total lipid is composed of neutral fats plus phospholipid plus free cholesterol plus ester cholesterol plus cholesterol ester fatty acids (the latter calculated from the ester cholesterol fraction). All values for lipids have been expressed in terms of milligrams per hundred grams of leukocytes, not in terms of cubic centimeters of blood. Hence the value for a lipid of the leukocytes bears no relation to the total white cell count, which in leukemia was found to vary between 40,000 and several hundred thousand cells per cubic millimeter. In myelogenous leukemia granulocytes were found to compose almost 100 per cent of the total leukocyte content of the blood, and in lymphatic leukemia the leukocytes of the blood were found to be practically all lymphocytes, immature, adult and degenerate forms being present in both instances.

Lipid Composition of White Blood Cells in Nine Patients with Chronic Myelogenous Leukemia and in Eight with Chronic Lymphatic Leukemia and in Thirty Normal Adults *

Condition of Subjects from Whom Leukocytes Were Obtained	Minimum Value	Maximum Value	Mean	Standard Deviation†
Total Lipid				
Chronic myelogenous leukemia	1,272	2,782	1,978	464
Chronic lymphatic leukemia	760	1,504	1,092	226
Normal	688	2,142	1,447	422
Total Fatty Acids				
Chronic myelogenous leukemia	718	1,800	1,170	326
Chronic lymphatic leukemia	492	718	625	75
Normal	357	1,390	830	273
Neutral Fat				
Chronic myelogenous leukemia	0	780	204	208
Chronic lymphatic leukemia	0	398	236	148
Normal	0	608	209	212
Total Cholesterol				
Chronic myelogenous leukemia	226	442	329	75
Chronic lymphatic leukemia	130	323	200	72
Normal	111	492	320	95
Ester Cholesterol				
Chronic myelogenous leukemia	0	120	57	42
Chronic lymphatic leukemia	0	103	35	33
Normal	0	280	82	73
Free Cholesterol				
Chronic myelogenous leukemia	170	435	272	74
Chronic lymphatic leukemia	97	253	165	49
Normal	72	452	238	95
Phospholipid				
Chronic myelogenous leukemia	1,000	1,840	1,403	252
Chronic lymphatic leukemia	348	780	591	157
Normal	442	1,280	869	281

* The results are expressed in milligrams of lipid per hundred grams of leukocytes.

† Calculated from the formula, $\theta = \sqrt{\Sigma (x)^2/\eta}$, in which θ represents the standard deviation, Σ a summation symbol, x the variation of each value from the mean and η the total number of readings.

As shown in the table, the values obtained for the total lipid of the white blood cells in chronic myelogenous leukemia vary between 1,272

and 2,782 mg. per hundred grams with an average of 1,978 mg. The values for the total lipid of the white cells in chronic lymphatic leukemia are only about one half as great, varying between 760 and 1,504 mg., with a mean of 1,092 mg., per hundred grams. The granulocytes of the blood in chronic myelogenous leukemia thus contain twice as much total lipid as the lymphocytes in lymphatic leukemia.

Both types of cells contain total lipid in amounts within or almost within the range found in normal adults. The normal values for the total lipid of the leukocytes varies between 688 and 2,142 mg., with a mean of 1,447 mg., per hundred grams. It may be seen that in chronic lymphatic leukemia the values of the total lipid of the leukocytes lie in the lower part of the normal range while in chronic myelogenous leukemia they lie in the upper part. And there is little overlapping. A few of the highest values in the lymphatic group are of the same order of magnitude as a few of the lowest values in the myelogenous group, but for the most part the values in chronic lymphatic leukemia are distinctly below those in the myelogenous type.

The fact that although there is a distinct difference between the two types of chronic leukemia yet practically all the values are within the normal range suggests that the blood leukocytes in leukemia are normal cells merely multiplied in numbers. In previous communications [17] evidence was offered that the lymphocyte contains much less lipid than the polymorphonuclear leukocyte. If the leukocytes in lymphatic leukemia possess a metabolism similar to that of normal lymphocytes, whether immature, adult or degenerate, one may expect to find relatively low values for leukocytic total lipid in cases of this disease, in which nearly all the leukocytes present are lymphocytes. As shown in the table this is precisely the result obtained. On the other hand, if these cells were of a malignant type, coinciding with the conception of "cancer of the blood," one might reasonably expect to find high values for lipid. Malignant tissue has been found by many, for example, Yasuda and Bloor,[18] to contain increased amounts of phospholipid, cholesterol and even neutral fats. It appears that when a tissue passes from a normal to a malignant type of metabolism there occurs an increase in its lipid. In unpublished experiments I have been able to demonstrate this in a case of carcinoma of the uterine mucosa.

The total lipid of the leukocyte fraction of the blood in chronic lymphatic leukemia is thus low probably for the sole reason that there is a preponderance of lymphocytes in this fraction. In the same manner the relatively high total lipid of the leukocyte fraction in chronic myelogenous leukemia appears to be due to the high percentage of poly-

17. Boyd.[12] Boyd and Wilson.[13] Boyd and Stephens.[15]

18. Yasuda, M., and Bloor, W. R.: J. Clin. Investigation **11**:677, 1932.

morphonuclear cells in the buffy layer of the blood. In neither instance need one invoke any semblance of a malignant change in the leukocyte metabolism to explain the results encountered. From the point of view of their lipid content, the blood leukocytes in chronic leukemia appear to be analogous to the leukocytes found in conditions of health, the only difference being an increase in their numbers.

Total Fatty Acids.—The total of the fatty acids of the leukocytes was determined by saponifying an aliquot of the alcohol-ether extract, extracting the fatty acids and cholesterol therefrom, and oxidizing the lipids thus isolated. From the resultant value was subtracted the equivalent of the cholesterol as separately determined.[16] The total fatty acid fraction is composed of fatty acids derived from phospholipid, neutral fat and cholesterol ester. The "neutral fat" fraction may include fatty acids other than those in the form of triglycerides if such are present.

As shown in the table, the values for the total fatty acids of the white blood cells in chronic myelogenous leukemia range from 718 to 1,800 mg. per hundred grams, with an average of 1,170 mg. Again these values are about double those in chronic lymphatic leukemia, which vary between 492 and 718 mg., with a mean of 625 mg., per hundred grams. The values for the total fatty acids of the leukocytes of normal adults range from 357 to 1,390 mg. per hundred grams, a range which includes practically all of the leukemic values.

Variations in the total fatty acids are thus analogous to those in the total lipid. In chronic myelogenous leukemia the total fatty acid content of the white blood cells lies in the upper range of the normal, and in chronic lymphatic leukemia it lies in the lower range. An interpretation similar to that offered for total lipid appears to fit these facts, i. e., that the lymphocyte content of fatty acids is less than that of the granulocyte and that the differences in leukemia are due to the differences in the percentages of the types of cells present, not to any alteration in the metabolism of leukemic leukocytes.

Neutral Fat.—The neutral fat was determined by subtracting from the value for total fatty acids the value for phospholipid fatty acids and that for cholesterol ester fatty acids and transposing the value thus obtained for the residual fatty acids into milligrams of triglyceride or neutral fat. As the amount of neutral fat is calculated from four different experimental values, the experimental or personal error becomes much greater than in the calculation of that of any other lipid. Hence one expects to find more variation in the values of neutral fat.

Such is actually the case. In chronic myelogenous leukemia the values for neutral fat range from 0 to 780 mg. per hundred grams; in chronic lymphatic leukemia, from 0 to 398 mg. per hundred grams,

and in normal conditions, from 0 to 668 mg. per hundred grams. The mean values were, respectively, 204, 236 and 209 mg. per hundred grams, which express very well the fact that no significant difference is found between the leukocytes in the three types of conditions. Stephens and I [15] were unable to demonstrate any difference between the neutral fat content of the normal lymphocyte and that of the normal granulocyte. In fact, the only consistent change in leukocytic triglycerides which I have so far encountered was an increase following parturition,[9] which I interpreted as indicative of a scavenger action of the white blood cells in removing débris fat from the involuting uterus.

Total Cholesterol.—The variations in the total cholesterol have been listed in the table. This lipid was estimated [19] by saponifying an aliquot of the alcohol-ether extract and extracting the cholesterol, which was then precipitated with digitonin, washed and oxidized. The total cholesterol is composed of free cholesterol plus cholesterol derived by saponification of cholesterol esters. In the blood leukocytes most of the cholesterol is in the free form.

In chronic myelogenous leukemia the values for total cholesterol vary between 226 and 442 mg. per hundred grams, with a mean of 329 mg. These values are approximately 50 per cent higher than those in the chronic lymphatic group, which range from 130 to 323 mg., with a mean of 200 mg., per hundred grams. In normal conditions in adults the values for leukocytic total cholesterol vary between 111 and 492 mg., a range which includes all values found in both types of chronic leukemia.

The differences in total cholesterol are thus not so striking as are those in total lipid and total fatty acids. In general, there tends to be less cholesterol in the blood leukocytes in the lymphatic and more in the myelogenous leukemia. Since all the values fall within the normal range it is probable that what differences exist are due again to the differences in the percentages of the types of leukocytes present, the lymphocyte containing less cholesterol than the myeloid cell. Stephens and I [15] found that the normal lymphocyte contains less free cholesterol than the normal neutrophil but were unable to make any distinction in regard to ester cholesterol. Hence one expects relatively less difference between the values for total cholesterol.

Ester Cholesterol.—There was very little ester cholesterol in the majority of the leukocyte fractions analyzed, as may be seen in the table. Ester cholesterol was estimated by subtracting from the value for total cholesterol that for free cholesterol as determined in a separate aliquot. Ester cholesterol is usually reckoned as constituting about 60 per cent of the cholesterol ester fraction of the total lipid.

19. Boyd.[16]

In chronic myelogenous leukemia the values for ester cholesterol range from 0 to 120 mg. per hundred grams; in chronic lymphatic leukemia, from 0 to 103 mg., and in normal conditions in adults from 0 to 289 mg. The mean values are, respectively, 57, 35 and 82 mg. per hundred grams. Superficially these mean values may appear to demonstrate significant differences, but it will be obvious from a survey of the means plus standard deviations that no real difference may be claimed. Ester cholesterol, like neutral fat, varies considerably. The only approach to any consistent change which I have noted is a tendency for ester cholesterol to be low during infection and postoperatively when the patient is recovering or about to recover and to be high when the patient is not recovering,[11] and even in this respect there are many exceptions. From the present data the conclusion may be made that there is no appreciable difference in the ester cholesterol of the blood leukocytes in either chronic lymphatic or chronic myelogenous leukemia.

Free Cholesterol.—The free cholesterol was determined by precipitation from an unsaponified aliquot of the extract, washing the precipitate and oxidizing it. There is very little experimental error involved in the determination of the free cholesterol.

As shown in the table the values for free cholesterol vary from 170 to 435 mg. per hundred grams in chronic myelogenous leukemia, the mean being 272 mg. These values are in general about 75 per cent higher than those in chronic lymphatic leukemia, in which the extremes are 97 and 253 and the mean 165 mg. per hundred grams. The normal range, extending from 72 to 452 mg., with an average of 238 mg., per hundred grams, includes all the values found both in chronic myelogenous and in chronic lymphatic leukemia. Thus in chronic lymphatic leukemia the free cholesterol of the white blood cells lies in the lower range of the normal, and in chronic myelogenous leukemia it lies in the higher range. This may likewise be explained by the predominant type of cell present and not by any change in the metabolism of the blood leukocytes in leukemia.

Phospholipid.—The most consistent and the most pronounced difference between the blood leukocytes in the two varieties of chronic leukemia occurs in the phospholipid fraction. The phospholipid was determined by precipitation with acetone and magnesium chloride followed by oxidation of the solutes in the moist ether solution of this precipitate. It is recognized that this procedure determines all of the lecithin and cephalin and part or most of the di-aminophospholipids.[16b]

In chronic myelogenous leukemia the values for leukocytic phospholipid vary between 1,000 and 1,840 mg. per hundred grams, with a mean of 1,403 mg. All of the values in chronic myelogenous leukemia are substantially higher than all of the values in chronic lymphatic leu-

kemia. On the average they are about two and a half times higher. In chronic lymphatic leukemia the range is from 348 to 780 with a mean of 591 mg. per hundred grams. The results indicate a distinct difference between the two diseases.

In the case of phospholipid a fair proportion of the values in leukemia are beyond the range of the normal for adults. Several of the values in chronic myelogenous leukemia are higher than those found for healthy adults while some of the values in chronic lymphatic leukemia are lower than those for normal adults. The normal range is from 442 to 1,380 mg., with a mean of 869 mg., per hundred grams.

The results are in accord with previous findings (Boyd and Wilson [13] and Boyd and Stephens [15]) in suggesting that the lymphocyte contains a much smaller amount of phospholipid than the granulocyte. In terms of Bloor's hypothesis that phospholipid content varies directly as physiologic activity, these results suggest that the granulocyte is a more active cell than the lymphocyte. This conclusion is also in line with the studies of oxygen consumption made by Soffer and Wintrobe,[1] as previously mentioned.

COMMENT

In brief it may be stated that the phospholipid and free cholesterol in the blood leukocytes are decreased in chronic lymphatic leukemia and increased in chronic myelogenous leukemia, and, of the two, the most marked change occurs in the phospholipid fraction. As a result of these differences, total fatty acids and total lipid are lower in the lymphatic than in the myelogenous type. Owing to the difference in free cholesterol, the total cholesterol in the leukocytes is lower in chronic lymphatic leukemia than in chronic myelogenous leukemia. There are no consistent changes in the neutral fat or in the cholesterol esters, the latter being low in most blood leukocytes.

The range of values for the total lipid in the leukocytes of normal adults is sufficient to include all the values found in leukemia. In general, the values in chronic lymphatic leukemia fall in the lower part of the normal range, and the values in chronic myelogenous leukemia, in the higher part. When this fact is compared with the previous observations that the lipid of the granulocytes tends to be higher than that of the lymphocytes, it appears that the differences in leukemia are due to differences in the relative percentages of lymphatic and myeloid types of cells in the buffy layer of blood, and not to a change in the metabolism of the blood leukocytes in leukemia.

A CASE OF ACUTE MYELOID LEUKEMIA

A sample of blood was obtained from a patient with acute myeloid leukemia. The predominant type of leukocyte was a very immature granulocyte of the myeloblastic variety, which is difficult to distinguish from the lymphoblast. It is

of interest that analysis of the lipid composition of the leukocytes revealed values similar to those in chronic lymphatic leukemia rather than to those in chronic myelogenous leukemia. The following values were obtained: total lipid, 976 mg. per hundred grams; total fatty acid, 570; neutral fat, 137; total cholesterol, 179; ester cholesterol, 0; free cholesterol, 179; phospholipid, 660. These results may suggest that lipid metabolism is of a similar type in immature forms of both the lymphocyte and the granulocyte or that the immature granulocyte is a less active cell than the mature granulocyte as found in the studies of oxygen consumption made by Glover, Daland and Schmitz.[2]

TWO CASES OF HODGKIN'S DISEASE

In two cases of Hodgkin's disease the lipid composition of the blood leukocytes was examined, and in neither case was the concentration of any lipid materially outside the range found in leukocytes under normal conditions. The values in these two cases were, respectively: total lipid, 1,471 and 2,089 mg. per hundred grams; total fatty acids, 734 and 1,178; neutral fat, 0 and 0; total cholesterol, 372 and 319; ester cholesterol, 12 and 0; free cholesterol, 360 and 319; phospholipid, 1,090 and 1,770.

SUMMARY

The lipid composition of the white blood cells was determined by oxidative micromethods for nine patients with chronic myelogenous leukemia, eight with chronic lymphatic leukemia, one with acute myeloid leukemia, two with Hodgkin's disease and thirty normal adults.

All the values obtained fall within the normal range, but several significant differences between the two types of chronic leukemia are exemplified in the following mean values (in milligrams per hundred grams of leukocytes):

	Chronic Myelogenous Leukemia	Chronic Lymphatic Leukemia	Normal Conditions in Adults
Total lipid	1,978	1,092	1,447
Total fatty acids	1,170	625	830
Neutral fat	204	236	209
Total cholesterol	329	200	320
Ester cholesterol	57	35	82
Free cholesterol	272	165	238
Phospholipid	1,403	591	869

It is suggested that the differences between the two types of chronic leukemia are due to the differences in the percentages of the types of leukocytes present, the polymorphonuclear leukocyte tending to have a greater lipid content than the lymphocyte, and that no abnormal change occurs in the lipid metabolism of the blood leukocytes in leukemia.

In a case of acute myeloid leukemia the lipid content of the white blood cells was relatively low, and in two cases of Hodgkin's disease it was relatively high.

CHEMOTROPIC REACTIONS OF POLYMORPHONUCLEAR LEUKOCYTES TO VARIOUS MICRO-ORGANISMS

A COMPARISON

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In experiments on the chemotropic reaction of human polymorphonuclear leukocytes in vitro, it was found that while these cells were attracted only moderately by dried white blood corpuscles and even less by paraffin wax and by fragments of glass, they were strongly attracted by Staphylococcus albus and certain other bacteria.[1] These results led us to inquire whether all types of bacteria attract polymorphonuclear leukocytes in vitro, and whether some types attract more strongly than do others. We accordingly selected a number of micro-organisms of widely different nature and pathogenicity and determined quantitatively the chemotropic reaction to each.

METHOD

A minute clump of bacteria was transferred from an agar slant or from a centrifuge tube, in which they had been washed, to a glass slide. There, after drying, they formed a flat object from 50 to 150 microns in diameter. A drop of blood from the finger was then placed on a coverslip and lowered on the mass of bacteria in such a way that the blood spread evenly between the slide and the coverslip. The preparation was sealed with petrolatum and observed under the high power of the microscope, at 37 C.

By means of a drawing ocular, the image of a microscopic field containing part of the bacterial clump was projected on paper, and the position of each polymorphonuclear leukocyte in the field was recorded at intervals of one minute usually for half an hour. A record obtained in this way may be found in a recently published paper.[1]

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1. McCutcheon, M.; Wartman, W. B., and Dixon, H. M.: Arch. Path. **17:** 607, 1934.

The chemotropic response of each leukocyte is evaluated by measuring on the graphic record, first, the net approach [2] of the leukocyte to the bacteria in a given time, and second, the total path traversed by the cell in the same time. The ratio of these two distances is taken as the measure of the chemotropism. It is evident that the more directly the cell approaches the bacteria, the higher will be the ratio, +1.00 representing maximal positive chemotropism. If the cell moves away from the bacteria, the net approach, and consequently the chemotropism, will have a negative sign, —1.00 representing maximal negative chemotropism. This method of measuring chemotropism has been described in greater detail elsewhere.[3]

RESULTS

In table 1 are the measurements of a representative experiment in which Staphylococcus albus was used as the source of attraction. During a one-half hour period polymorphonuclear leukocytes appeared in the microscopic field. The path of each cell was recorded from its first appearance until it made contact with the bacteria or until the end of the period of observation. In the table are given the net

TABLE 1.—*Experiment Illustrating the Computation of Values of Chemotropism* *

Cell	Net Approach, Mm.	Total Path, Mm.	Value of Chemotropism
1	47	51	0.92
2	41	48	0.85
3	54	62	0.87
4	57	66	0.86
5	49	65	0.75
6	77	91	0.85
7	98	105	0.89
8	80	85	0.94
9	71	76	0.93
10	40	45	0.89
11	56	63	0.89
12	47	66	0.71
13	36	38	0.95
14	65	77	0.84
15	58	67	0.87
16	39	44	0.89
17	64	92	0.70
18	0	31	0.00
Mean			0.81

* Staph. albus was used as the source of attraction. During a half hour's observation eighteen polymorphonuclear leukocytes appeared in the field. Distances are given in millimeters as measured on the graphic record. The "net approach" of each leukocyte is the difference between the distance from the bacteria at the first and that at the last observation. The "total path" is the total distance traversed in the same time. The value of the chemotropism is the ratio of these two quantities.

2. The net approach of a leukocyte is the difference in distance to the nearest point of the bacterial clump at the first and at the last observation. For instance if a leukocyte at the first observation lies 92 mm. from the bacteria (as measured on the graphic record) and at the last observation is in contact with the bacterial mass, the net approach is 92; if, however, the leukocyte has not made contact at the last observation but is located 12 mm. from the edge of the clump, the net approach is 80. One millimeter on the graphic record equals approximately 2.5 microns of actual distance.

3. Dixon, H. M., and McCutcheon, M.: Arch. Path. **19**:679, 1935.

approach and the total path of each cell, measured on the graphic record in millimeters, these distances being proportional to the number of microns actually traversed. The ratio of the net approach to the total path gives the value of the chemotropism, which is recorded in the last column. The range of chemotropic values is from + 0.70 to + 0.95, except for cell 18, which showed no net approach and consequently has a value of zero. The mean value of the chemotropism of 18 cells is + 0.81.

The results of forty-four such experiments are summarized in table 2. The micro-organisms tested included common pyogenic cocci, such nonpyogenic organisms as typhoid bacilli (smooth strain) and tubercle bacilli (bovine III and R1 strains), Micrococcus tetragenus, the virulent yeast Torula histolytica and several other yeasts. The

TABLE 2.—*The Values of Chemotropism with Various Micro-Organisms* *

Micro-Organism	Experiments	Leukocytes	Mean Value of Chemotropism
M. tetragenus	5	101	+0.83
Pneumococcus	2	46	+0.83
Str. haemolyticus	4	87	+0.81
Staph. albus	9	157	+0.81
Staph. aureus	6	120	+0.80
Bact. typhosum	6	98	+0.78
Miscellaneous yeasts	4	91	+0.78
M. tuberculosis	4	85	+0.77
T. histolytica	4	86	+0.57
Controls	12	112	+0.02

* The values are seen to lie within a narrow range except in the case of T. histolytica. The control cells were not subjected to any known source of attraction; their chemotropism approximates zero.

typhoid bacilli and, in one experiment, Staph. aureus were killed by heat. In the other experiments the micro-organisms were simply dried on the slide.

The mean value of chemotropism is given for each micro-organism in the last column of table 2. It will be observed that, except for experiments with T. histolytica, these values lie close together, the range being from + 0.83 to + 0.77.

In sharp contrast to the strongly positive chemotropism shown by leukocytes near the focus of attraction was the behavior of cells at a distance. Here, in the absence of known sources of attraction, locomotion was at random, and the value of chemotropism approximates zero. In our experiments control leukocytes were observed at distances of from 4 to 8 mm. (actual distance) from the bacteria; the mean value of the chemotropism was + 0.02 (bottom row of table 2).

The question now arises: Are the differences between the several micro-organisms significant? From column 3 of table 2 it looks as if they are not except in the case of T. histolytica.

To test this impression, our data were analyzed by the method of χ^2, for a description of which the reader is referred to the article by Dunn.[4] From values such as are given in the last column of table 1, frequency classes were constructed according to the intensity of the chemotropic response. For example, in the first class is placed the number of leukocytes with values of chemotropism from -1.00 to $+0.60$; in the second class, the number of those with values between $+0.61$ and $+0.70$, and so on, as is shown in table 3. For comparison with these observed frequencies are given expected frequencies in parenthesis; from the differences between observed and expected frequencies, values of χ^2 have been computed, and from these, in turn, the probabilities that the differences are due to random sampling.[5]

TABLE 3.—*The Frequency Distribution of Leukocytes* *

Micro-Organism	60 and Less	61 to 70	71 to 80	81 to 90	91 to 100	Total	χ^2	p
M. tuberculosis.....	14 (11)	9 (10)	10 (16)	24 (25)	28 (24)	85	3.88	0.43
Bact. typhosum.....	14 (12)	11 (11)	20 (18)	31 (29)	22 (28)	98	1.98	0.73
Staph. albus.....	13 (19)	21 (18)	25 (29)	58 (46)	40 (45)	157	6.63	0.16
M. tetragenus.....	8 (13)	9 (11)	21 (18)	31 (30)	32 (29)	101	3.13	0.55
Staph. aureus.....	12 (15)	11 (14)	28 (22)	28 (35)	41 (35)	120	5.31	0.26
Miscellaneous yeasts.	9 (11)	15 (10)	20 (17)	28 (27)	19 (26)	91	5.32	0.26
Pneumococcus.....	4 (6)	5 (5)	6 (8)	12 (13)	19 (13)	46	4.02	0.42
Str. haemolyticus....	10 (11)	5 (10)	17 (16)	22 (25)	33 (25)	87	5.57	0.23
T. histolytica.....	24 (11)	12 (10)	12 (16)	21 (25)	17 (25)	86	19.92	0.00
Total.....	108	98	159	255	251	871		

* The leukocytes have been grouped according to their chemotropic reactions into five frequency classes, the limits of which are stated in the top row. In each group is given the observed frequency compared with the expected frequency (in parenthesis), computed as described in the text. The values of p (last column) represent the probability (on the basis of 1.00 as certainty) that equal or greater differences in distribution would be obtained by random sampling. Only in the case of T. histolytica is the distribution significantly different.

These probabilities are listed in the last column of table 3 as values of p. For example, for Mycobacterium tuberculosis the value is 0.43. This figure means that 43 times in 100 differences between observed and expected distributions as great as or greater than found here would be obtained by random sampling. A value of p above 0.05 (i. e., 5 times out of 100) is usually regarded as not significant. It is apparent,

4. Dunn, H. L.: Physiol. Rev. **9**:275, 1929. See especially page 314.

5. The expected frequency is computed by dividing the class total by the grand total of all the cells and multiplying by the number of cells observed in experiments with a given micro-organism. For example, these figures are, for class I of Mycobacterium tuberculosis, $108 \div 871 \times 85 = 11$. Values of χ^2 are computed as follows: In each class, the square of the difference of the expected and observed frequencies is divided by the expected frequency. Thus for the first class of M. tuberculosis $(14\text{-}11)^2/11 = 0.82$. In the same way the other frequency classes of M. tuberculosis are evaluated. The sum of these values for the five classes is 3.88, the value of χ^2. Values of p corresponding to values of χ^2 have been obtained from a graph in Dunn's paper.[4]

therefore, that with the single exception of T. histolytica none of the differences in this table between observed and expected frequencies is probably significant, and we may regard the reaction of the leukocytes to the several micro-organisms as practically equal in the present experiments.

With T. histolytica χ^2 is equal to 19.92 and $p = 0.00$, indicating that the difference in chemotropism with T. histolytica and with the other micro-organisms is not due to chance. This difference is due to the fact that, though during the early part of the experiments leukocytes were strongly attracted by the yeast, after about half an hour 14 of the 86 leukocytes that were observed moved away from the yeast in a nearly straight line. Such cells consequently had a negative value of chemotropism. Negative cells were rarely observed in the case of the other micro-organisms (at least during the first hour of observation); consequently in the case of T. histolytica the distribution of leukocytes in table 3 differs from those with the other micro-organisms. The explanation for the behavior of leukocytes toward T. histolytica must await further experiments.

LITERATURE

Earlier experiments on chemotropic attraction by bacteria were usually made by placing a suspension of the micro-organisms in capillary tubes, which were then inserted into the tissues of animals or into suspensions of leukocytes in vitro. As previously pointed out,[1] this method was likely to be affected by such errors as would make invalid the comparison of the numbers of leukocytes in different tubes. There is no doubt, however, that leukocytes were in fact attracted by the micro-organisms. Thus Leber[6] reported positive chemotropism by staphylococci; Buchner,[7] by proteins of Friedländer's bacillus, Pyocyaneus and typhoid bacilli. Beer yeast and staphylococci,[8] various bacteria (including Bacterium typhosum) and bacterial filtrates[9] and anthrax bacilli[10] were found to attract leukocytes. Negative chemotaxis (or absence of chemotaxis) was reported[9] in the case of young cultures of Bacillus cholerae-gallinarum. Massart[11] found that, with certain exceptions, more leukocytes entered capillary tubes containing nonvirulent than those containing virulent micro-organisms, and that chemotaxis

6. Leber, T.: Fortschr. d. Med. **6**:460, 1888; cited by Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925, p. 275.

7. Buchner, H.: Berl. klin. Wchnschr. **27**:673, 1890.

8. von Sicherer, O.: Centralbl. f. Bakt. **26**:360, 1899.

9. Gabritschevsky, G.: Ann. Inst. Pasteur **4**:346, 1890.

10. Pekelharing, C. A.: Semaine méd. **9**:184, 1889.

11. Massart, J.: Ann. Inst. Pasteur **6**:321, 1892.

to virulent bacteria was increased by immunization. More recently, under the microscope, Comandon [12] observed avian leukocytes moving directly toward certain hematozoa of birds, and Schulz [13] observed attraction by colon bacilli. In Meier's [14] experiments, living pyogenic bacteria were able to attract avian leukocytes from a distance of several millimeters, but dead bacteria did not do so. Avian tubercle bacilli, whether living or dead, did not attract cells from such a distance.

COMMENT

From this survey of the literature and from our own experiments we conclude that polymorphonuclear leukocytes in vitro display positive chemotropism to micro-organisms in general (though apparent exceptions have been noted by others). Does this generalization hold in vivo as well? It is likely that it does, in spite of the fact that collections of polymorphonuclear leukocytes are not usually seen in tissues infected with such organisms as tubercle and typhoid bacilli. Yet it has been observed [15] that during two different stages of the evolution of experimental tuberculosis, polymorphonuclears are attracted vigorously; during other stages these cells may disappear. The rule in all or most infections seems to be that at first polymorphonuclears are attracted; later, mononuclears replace them partly or altogether.[16]

An apparent exception is infection with T. histolytica, in which polymorphonuclear leukocytes have been reported to be completely absent from the infected tissues.[17] This observation is particularly interesting in view of our own observation of negative chemotropic response on the part of some cells. Yet even to this organism, as stated, we found that during the early part of the experiment leukocytes were vigorously attracted, and it is possible that there may be a similar short period of attraction in vivo.

In conclusion, we suggest that in vivo as well as in vitro polymorphonuclear leukocytes are attracted, at least potentially, by micro-organisms in general, but that their chemotropic response may sometimes be masked. Thus, (1) leukocytes may be so damaged that they are incapable of locomotion and consequently cannot exhibit chemotropism, or, as suggested by Menkin,[18] (2) certain micro-organisms may not

12. Comandon, J.: Compt. rend. Soc. de biol. **80**:314, 1917.

13. Schulz, E.: Ztschr. f. d. ges. exper. Med. **84**:609, 1932.

14. Meier, R.: Ztschr. f. ges. exper. Med. **87**:283, 1933.

15. Lurie, M. B.: J. Exper. Med. **60**:163, 1934. Woodruff, C. E.: Am. J. Path. **10**:739, 1934.

16. Opie, E. L.: Arch. Int. Med. **5**:541, 1910.

17. Freeman, W., and Weidman, F. D.: Arch. Neurol. & Psychiat. **9**:589, 1923. Freeman, W.: Tr. Am. Neurol. A. **56**:203, 1930.

18. Menkin, V.: Proc. Soc. Exper. Biol. & Med. **32**:162, 1934.

irritate the tissues and therefore fail to bring about emigration of leukocytes, or (3) leukocytes may be attracted only during certain (usually early) stages of an infection.

SUMMARY

Human polymorphonuclear leukocytes in vitro under certain experimental conditions exhibited strongly positive chemotropic response to all of a number of micro-organisms (including staphylococci, streptococci, pneumococci, tubercle bacilli, typhoid bacilli and T. histolytica) differing greatly in pathogenicity and virulence. In the intensity of the response to the several micro-organisms no significant differences were found except as to T. histolytica. The relation of chemotropism in vitro to that in infected tissues is briefly discussed.

TERATOMA

AN EXPLANATION OF ITS CAUSE BASED ON THE ORGANIZER THEORY OF EMBRYOLOGY

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Many conflicting theories as to the etiology of teratoma have been formulated. Ewing [1] (1922) ventured the statement that "no single mode of origin may be adduced to account for all the various forms and sites" at which teratoma may occur. Yet the theory of "organizers," as elaborated by Spemann [2] (1918), when applied to this peculiar tumor, gives a consistent and complete theoretical explanation which covers the variation in morphology and the wide distribution that have so commonly been observed.

A brief catalog of the general distribution of teratoma indicates the complexity of this problem. The following list is by no means a complete summary of all the sites that have been noted, but it is representative enough to show the theoretical conditions which must be met. No attempt is made here to give all the sources of information, since that would be far beyond the practical scope of this work.

Brain: Frontal lobe, tela choroidea III, tuber cinereum, left cerebral hemisphere, centrum ovale, cerebellum, cerebellopontile angle, pituitary body, pineal body, arachnoid and dura.

Spinal Cord: Arachnoid (multiple tumors from the cervical region to the cauda equina).

Head: Conjunctival sac, nasal septum, lacrimal glands, temporal bone, orbit, antrum, base of the tongue, throat, face, gums, external auditory meatus and tonsil.

Neck: Thyroid and larynx.

Thorax: Pulmonary tissue, anterior mediastinum, pericardium and mammary gland.

Abdomen: Gastrosplenic ligament, peritoneum (multiple), retroperitoneal region, kidneys, pararenal region, uterus, ovaries, testes, gonads in cases of tubular hermaphroditism, undescended testicle and paragenital, presacral, lumbosacral, sacrococcygeal and postrectal regions.

From the University of Georgia School of Medicine.

1. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.

2. Spemann, H.: Arch. f. Entwcklngsmechn. d. Organ. 43:448, 1918.

Pelvis: Inguinal region, penis, urinary bladder, gluteal region, right groin and right side of the perineum.

Umbilical Region: Umbilical cord.

Placenta: Only two cases on record; three germ layers involved; one teratoma located 3 cm. from the insertion of the cord.

The common sites of predilection are (1) the gonads, (2) the sacrococcygeal region and (3) the branchiogenic region. Only three regions are apparently free: the limbs, the heart and the liver.

CRITIQUE OF OLDER THEORIES

No one will take exception to the view that the cause of teratoma is to be sought on embryologic grounds. Teratoma is certainly not directly due to bacterial infection or to accident, such as fracture of the femur. With this basic line of departure, it remains only to establish the most likely period of derangement of developmental factors and to seek a causal factor which could be responsible. All previous theories have been more or less biased by a static, spatial or morphologic concept of embryology, which naturally limited and fixed the developmental pattern. The wide range of form and the extensive distribution of teratoma must of course be the principal consideration in testing the plausibility of any hypothesis.

1. *Maturation and Fertilization Period.*—The polar body theory of Marchand [3] (1894) and Ribbert [4] (1892) has little in its favor. Ewing [5] (1911) has reviewed the subject. The outstanding facts against it are (1) the rare experimental evidence that polar bodies may be fertilized, (2) the occurrence of multiple teratoma in excess of three polar bodies and (3) the common occurrence of both the host and the parasites in the same membranes, which must premise a fusion of embryos and membranes.

2. *Cleavage Period.*—The blastomere theory of Bonnet [6] (1899) is based on the following hypothetic premises: (1) splitting off and migration of blastomeres, (2) retention of totipotence of such blastomeres, (3) fusion of the membranes in certain forms and (4) multiple splitting and symmetric shifting against cellular barriers in the case of multiple teratoma.

Outstanding against the Bonnet hypothesis are the following facts: The results of experimental embryology in lower animals indicate that blastomeres do not long retain their totipotence when isolated. This is

3. Marchand, F.: Berl. klin. Wchnschr. **1**:36, 1894.

4. Ribbert, H.: Arch. f. path. Anat. **130**:249, 1892.

5. Ewing, J.: Surg., Gynec. & Obst. **12**:230, 1911.

6. Bonnet, M.: Ergebn. d. Anat. u. Entwcklngsgesch. **9**:820, 1899.

seen in the amphioxus and in the starfish. The premised splitting of blastomeres, originally invoked to account for identical twins, has been abandoned since the mechanism of polyembryony has been observed in the armadillo.

Furthermore, shifting of the blastomeres in mammalian development, should it occur, must lead to some very unusual conditions. Early shifting of blastomeres from the inner cell mass to new positions in the germinal vesicle might produce either free or included twins enclosed in either separate or common amnions, but shifting of blastomeres within the trophoblastic cavity cannot possibly account for the development of an external teratoma in the sacrococcygeal region, as indicated by Budde[7] (1921).

3. *The Cell Rest Theory.*—This theory is concerned with a comparatively late period of development and involves inclusion of the germinal layers, delayed closure, invagination and pluripotential cells (Cohnheim,[8] 1877; Meyer,[9] 1905; Ross,[10] 1932). This view, invoked particularly to account for the branchiogenic tridermal cysts (Borgioli,[11] 1934) must premise a late dedifferentiation and a redifferentiation of tissue, i. e., nerve tissue from dermal ectoderm. No causal factor has been indicated. This hypothesis is hardly applicable to a deep-seated teratoma of the gonadal region or to a distant teratoma of the cord and placenta (Haendly,[12] 1923; Küster,[13] 1928).

4. *Parthenogenesis of Germinal Cells.*—This theory of parthenogenesis (Waldeyer,[14] 1872) within the ovary, testis or ovotestis (Langhans,[15] 1887), rete (Adami,[16] 1909) or wolffian duct (Cavazzani,[17] 1907) or Müller's duct (Kossman, cited by Ewing[5]) offers an enticing explanation. It is based on a predilection of teratoma for these sites and on the observation that eggs in atretic follicles in mice, rats, guinea-pigs and man undergo parthenogenic cleavage. Loeb[18] (1912) stated

7. Budde, M.: Beitr. z. path. Anat. u. z. allg. Path. **68**:512, 1921.

8. Cohnheim, J.: Vorlesung ueber allgemeine Pathologie, Berlin, A. Hirschwald, 1877.

9. Meyer, R.: Ergebn. d. allg. Path. u. path. Anat. **9**:2, 1905.

10. Ross, J. M.: J. Path. & Bact. **35**:563, 1932.

11. Borgioli, V. A.: Valsalva **10**:444, 1934; abstr., Am. J. Cancer **23**:643, 1935.

12. Haendly, P.: Arch. f. Gynäk. **116**:578, 1923.

13. Küster, J.: Arch. f. Gynäk. **133**:93, 1928.

14. Waldeyer, W.: Arch. f. path. Anat. **55**:132, 1872.

15. Langhans, T.: Deutsche Chir. (Abt. B) **50**:414, 1887.

16. Adami, J. G.: A Textbook of Pathology, Philadelphia, Lea & Febiger, 1909.

17. Cavazzani, T.: Beitr. z. path. Anat. u. z. allg. Path. **41**:413, 1907.

18. Loeb, L.: Ztschr. f. Krebsforsch. **11**:1, 1912.

the belief that these cells may continue to develop and form trophoblasts and thus account for the development of a chorionepithelioma on a teratogenous base. Kampmeier [19] (1929) questioned the interpretation of parthenogenesis, since no intermediate steps exist between early cleavage and the so-called trophoblastic vesicles. My own interpretation of the early stages is the same as that of Loeb, but I venture the caution that the "trophoblastic" stages which he has seen may have represented a true chorionepithelioma on a teratogenous base and that the two phenomena have nothing in common with regard to causation.

But were one to admit the theory in its entirety, not even the most orthodox of the parthenogenesists would hazard the suggestion of a migration of wandering and lost sex cells into such a site as the brain or the placenta.

ORGANIZER THEORY

In view of the untenable position of the foregoing hypotheses, I offer a new "organizer theory" to account for all teratomas. This organizer theory has been developed by Spemann and his co-workers in the field of experimental embryology. My own contribution is an application of the principle to the subject of teratoma. A simple and rational explanation is at hand which accounts for the variation, predilection and association of teratomas with chorionepitheliomas.

The outstanding features of the organizer hypothesis, as developed by Spemann, are as follows:

By transplanting the tissue from the dorsal lip of the blastopore, Spemann found that it is possible to "induce" secondary embryonic axes in the salamander (fig. 1 *A*). The organizer develops during the gray crescent stage in the egg, as shown by the fact that it may be destroyed by a hot needle. The direction in which the organizer acts is forward from the posterior part of the neural fold. After gastrulation has definitely occurred, further effect is from below under the influence of "late determiners." The effect is to "induce the neighboring tissues to follow the axial plan of organization." Organizers are progressive in their restricted ability to induce. Thus, the transplantation of a portion of the medullary plate to the blastocele induces the growth there of medullary plate.

Organizers are not preformed in the ovum; they develop. They are variable in amount. Their action is effective only during definite critical periods. Controlling factors in the development of the secondary embryo seem to be: (1) the level of the host's main axis at which the graft is applied, (2) the region from which the organizer is taken, (3) the distance of the primary from the secondary embryo and (4) the apparent restricted autonomy of some tissues when once established.

19. Kampmeier, O. F.: Am. J. Anat. **43**:45, 1929.

Experiments fully establish the fact that "presumptive" tissue can give rise to tissues other than those predestined by position. Thus any part of the blastula may become muscle or notochord. Mangold [20] (1923) has shown that presumptive ectoderm implanted just below the dorsal lip of the blastopore will be carried into the blastocele and will give rise to mesoderm, and, reciprocally, presumptive mesoderm will give rise to ectoderm. This has been definitely shown by transplants made from one species which bears little pigment to another species which is heavily pigmented. The individual tissues could be readily identified and the results analyzed (fig. *B*).

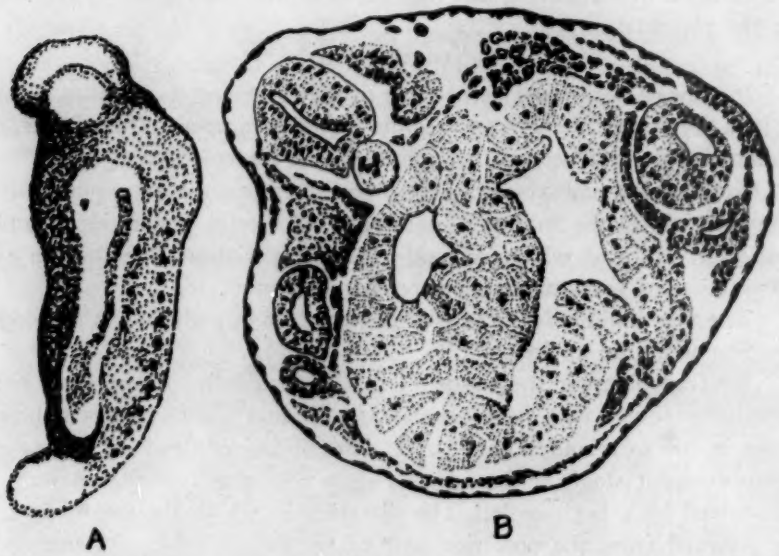

Fig. 1.—*A*, larva of an amblystoma showing a secondary embryo which was produced by the transplantation of the dorsal lip of the blastopore (redrawn from Spemann [2]). *B*, cross-section of a larva of an amblystoma showing the secondary and the primary embryonic axes (redrawn from Spemann [2]).

One further point of interest is that the polarity of the secondary embryo need not be the same as that of the primary embryo. Polarity may be reversed. Bilaterality, however, is specific.

That the reaction is not a simple contact reaction is shown by the fact that all tissues are not equally capable of "inducing." Ectodermal transplants do not have the same effect as transplants from the blasto-

20. Mangold, O.: Arch. f. mikr. Anat. u. Entwcklngsmechn. **100**:198, 1923.

pore. (The organizer then takes on the appearance of a "diffusible, labile agent" (Huxley and De Beer [21]).)

(To appreciate the problem fully one should refer to the papers of Spemann (1918), Mangold (1923), Bautzmann [22] (1929), Waddington [23] (1932) and Woollard [24] (1932) and to the reviews of Huxley and De Beer (1934).)

Before I develop my hypothesis as applied to teratoma, I wish to call attention to the masterly treatment of Budde (1921), who, on morphologic grounds alone, considered that maldevelopment of the primitive streak is responsible for the occurrence of teratoma in the sacrococcygeal region. It is significant that my hypothesis had been developed prior to a knowledge of the existence of his paper and that the same conclusions were reached by an entirely different approach.

An understanding of human development and of the homology of chordate development is essential to my point of view. (It is a generally accepted fact that the primitive knot, or Hensen's node, is the homolog of the dorsal lip of the blastopore, as seen in the salamander. Differentiation of the primary vertebrate axis occurs from this point. In man the knot is perforated by the so-called chordal canal, or, in the older concepts, by the "neurenteric canal." If now the organizer theory, as shown in the salamander (Spemann, 1918) and in the chick (Waddington and Schmidt,[25] 1933) is assumed to hold in man and if this labile, diffusible determiner is associated with Hensen's node, the distribution of teratoma and the predilection for specific sites become clear. Any derangement of the normal distribution of the organizer may induce the development of secondary embryonic axes at foreign sites. Frequency becomes a function of time, proximity and area; morphology becomes a function of time.)

In order to visualize the situation I offer a hypothetic topographic chart (fig. 2) representing the primordia or fields of the various organs on an embryonic shield, comparable to Heuser's embryo of the twentieth day. I have indicated the theoretical effect of the organizer by arrows. The enclosed arrows indicate the secondary embryonic axes established by derangement of the organizer. The proximity of the sacrococcygeal region, the gonadal region and the mesenterium commune to Hensen's node indicates the reason for the frequency of teratoma in these sites. The posterior migration of the primitive knot accounts

21. Huxley, J. S., and De Beer, G. R.: The Elements of Experimental Embryology, New York, The Macmillan Company, 1934, p. 134.

22. Bautzmann, H.: Naturwissenschaften **17**:818, 1929.

23. Waddington, C. H.: Phil. Tr. Roy. Soc., s.B **221**:179, 1932.

24. Woollard, H. H.: J. Anat. **66**:242, 1932.

25. Waddington, C. H., and Schmidt, G. A.: Arch. f. Entwcklngsmechn. d. Organ. **128**:522, 1933.

for a continued action in these zones. The broad extent of the branchiogenic fields on the primitive shield, with an even greater proximity in the earlier stages than here represented, accounts for the frequency of teratoma in this site.

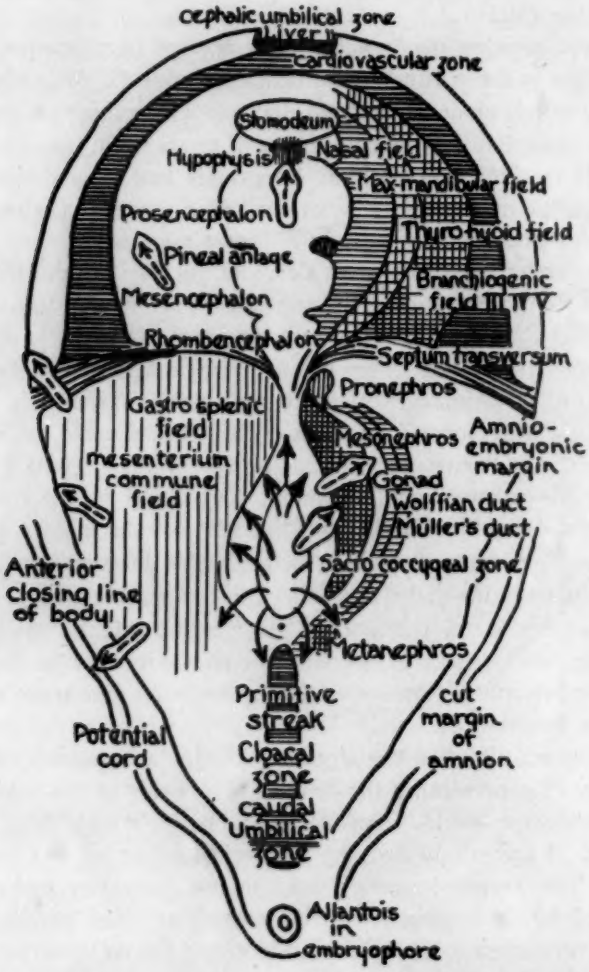

Fig. 2.—A hypothetic topographic chart showing the primordial fields in the 20 day human embryo. The heavy black arrows indicate the diffusion lines of the organizer from the primitive knot. The major sites of secondary axes are indicated by enclosed arrows. Note particularly the position of the liver and the heart.

The organizer may, however, act to the limit of the shield and produce either an included teratoma by incorporation within the anterior closing line of the body or, more rarely, an excluded teratoma, forced by growth onto the cord or placenta.

Multiple teratoma is simple to premise on this hypothesis. Its symmetry even indicates a symmetric diffusion of a causal agent.

The distance from the node and the tissue relations existing in the heart and liver indicate why these organs are free from teratoma. The limbs are late developments and hence are not invaded, except at their bases.

The one outstanding stumbling block to any theory of teratoma is the associated chorionepithelioma. It has been so embarrassing that Virchow's elusive theory of metaplasia has invariably been invoked. Hamdi [26] (1934) claimed that dedifferentiation and metaplasia may occur any place. I believe that I can furnish a simple, satisfactory and acceptable explanation based on genetic histology.

(The difficulty heretofore has been to account for a source of trophoblast cells. These, in man, necessarily lie on the outside of the ovum. Embryonic ectoderm and amnionic ectoderm arise de novo in the inner cell mass. But in the lower mammals, such as the rabbit, pig and cat, the amnionic cavity forms by a fusion of the two "somatopleures" over the embryonic shield. The amnionic ectoderm is therefore, for a time, essentially trophoblastic. Even in man this relationship is not entirely lost, since an amnionic (chorionic) duct has been repeatedly described. Furthermore, Florian [27] (1930) claimed to have identified typical Langhans cells in it, and he went further to show that the amnionic ectoderm, particularly at the posterior end of the shield, retains its invasive capacity in fashioning the embryophore or body stock. Here amnionic ectoderm behaves like abortive trophoblast.)

(Combining this point of view with that of organizers, the origin of a chorionepithelioma on a teratogenous base becomes relatively simple. The close proximity of the amnion to the embryonic shield provides a source for potential trophoblast cells. Furthermore, the close proximity of the amnio-embryonic junction (i. e., the junction of somatopleure and splanchnopleure) brings this tissue into juxtaposition with the site of the future urogenital ridges and indicates a reason for the predilection of chorionepithelioma on a teratogenous base for these organs, without, however, entirely limiting them to this zone. Kantrowitz' [28] (1934) report of a case of extragenital chorionepithelioma on a teratogenous base seems to be entirely acceptable. If his principle of destruction of teratoma by the invasive capacity of the chorion is further invoked, one has a consistent explanation of all chorionepitheliomas, and my hypothesis in this connection is rounded out.)

26. Hamdi, H.: Beitr. z. path. Anat. u. z. allg. Path. **93**:390, 1934.

27. Florian, J.: J. Anat. **64**:454, 1930.

28. Kantrowitz, A. R.: Am. J. Path. **10**:531, 1934.

The occurrence of teratoma in the so-called fusion lines of the body still awaits a rational explanation. The frequency of occurrence is due, not particularly to conditions which exist here that "cause" cell rests, but to the fact that the potential teratoma acts as a developmental "drag" and fixes the position of the line of fusion. Hence, internal and external teratomas, teratoids, dermoids and embryomas fall into a common category, and the monodermal, didermal and tridermal grades depend on (1) the time of development of the organizer defect, (2) the particular site at which it occurs, (3) the subsequent mechanical conditions with which the secondary embryo meets, (4) Pick's principle of predominance of one type of tissue and (5) cyclic endocrine factors for growth.

In conclusion, this view is not opposed to Stockard's [29] theory of developmental arrests (1921), since "faulty implantation" may well account for the presence of organizer defects.

SUMMARY

A new theory of the genesis of teratoma is proposed which is based on Spemann's organizer theory in embryology. Interference with the normal effect of the organizer may cause the production of secondary embryonic axes in the primitive shield and lead to the formation of a teratoma at any site. The observed frequency of teratoma in man is explained as a function of proximity of the potential fields to Hensen's node, namely, the sacrococcygeal region, the urogenital region and the branchiogenic field. No limit, however, is placed on the degree of diffusion of the factor; hence the occasional occurrence of teratoma in the brain, umbilicus and placenta. Mechanical interference prevents the occurrence of teratoma in the heart and liver, and the delay in the development of the limb buds until after the effective period of the organizer accounts for the nonoccurrence of teratoma in the latter sites. The association of choriocarcinoma on a teratogenous base in both genital and extragenital sites is explained on the hypothesis that the amnion is potentially chorion.

29. Stockard, C. R.: Am. J. Anat. **28**:115, 1921.

EMBOLIC PULMONARY LESIONS PRODUCED IN RABBITS BY HUMAN FAT CONTAINING FATTY ACIDS OR SOAPS

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Certain focal lesions in tissues and some systemic disorders are ascribed to deposits of lipids.[1] When the lesions are examined at a stage in which the lipid materials can be demonstrated by suitable stains or by chemical analysis, the etiologic correlation seems simple. After the tissue reactions have reduced the lipids to minute or chemically modified particles, the noxious substances are not so readily identified in the lesions. Even when the presence of lipids can be demonstrated, the exact nature of the substances giving the stimulus for the tissue reactions is not always understood. The development of granulation tissue in subcutaneous and other fat tissues, which Makai designated as lipogranulomatosis, has been described in a number of reports.[2] According to Abrikossoff, the earliest lesions are foci of necrosis of fat tissue and of subsequent saponification. Later, the inflammatory response is a growth of fibroblastic tissue containing lymphocytic and leukocytic exudates. Older lesions contain fat droplets, with marginal giant cells, and in chronic lesions the granulation tissue has become a fibrous scar with large vacuoles. Some authors have noted a resemblance of these lesions to the changes occurring in tuberculosis. Abrikossoff classified lipogranulomas on the basis of etiology into four groups: (1) tissue reactions following the subcutaneous injection of oil or fat, (2) traumatic reactions, (3) peri-inflammatory reactions in which fat tissues are involved by contiguous inflammation and (4) spontaneous reactions in which the cause of the lesions is uncertain.

Aided by the Winfield Peck Memorial Fund.

From the Henry Baird Favill Laboratory of St. Luke's Hospital.

1. Pick, L.: Am. J. M. Sc. **185**:453 and 601, 1933. Hirsch, Edwin F.: Arch. Path. **35**:665, 1935.

2. (*a*) Makai, E.: Klin. Wchnschr. **7**:2343, 1928. (*b*) Abrikossoff, A.: Centralbl. f. allg. Path. u. path. Anat. **38**:542, 1926. (*c*) Petri, E.: ibid. **37**:1, 1926. (*d*) Schlapobersky, W. J.: ibid. **53**:97, 1931. (*e*) Ansart, M. Bastos, and Got, J. d'Harcourt: Arch. f. klin. Chir. **172**:724, 1933. (*f*) Weber, Herbert: Zentralbl. f. Chir. **61**:1042, 1934. (*g*) König, Fritz: ibid. **61**:786, 1934. (*h*) Krauss, F.: ibid. **60**:1272, 1933. (*i*) Goldzieher, M. A.: Arch. Surg. **23**:690, 1931.

The main constituents of the lipids liberated into the subcutaneous tissues are the neutral fats. Opinions differ as to whether the neutral fats themselves, their split products—the fatty acids—or added substances, such as cholesterol and phosphatides, are the important elements in the stimulation of the tissue reactions. Wail [3] observed cellular infiltrations about subcutaneously injected human fat in the tissues of rabbits. Later, the tissue response included fibroblasts and giant cells. He noted, further, a gradual increase of cholesterol and phosphatide compounds in the injected fat. According to the view shared by Makai, von Quierke and Askanazy,[3a] the fat liberated by the necrotic cells is rapidly split by the lipases of the subcutaneous tissues into fatty acids. The content of fatty acids is the irritating factor which stimulates the lipophagic reaction. Ansart and Got,[2e] however, expressed the belief that the unsplit neutral fat provokes the inflammatory reaction. The tissue reactions to lipids extracted from tubercle bacilli have been studied by Sabin and her associates,[4] together with correlation of the chemical composition and the type of tissue response. The lipid material extracted from tubercle bacilli was fractioned into three portions. The first fraction, which was soluble in acetone, was a mixture of many fatty acids, so irritating that it stimulated every type of connective tissue cells. The other fractions, the phosphatides and the unsaponifiable material—the waxes—stimulated the monocytes. With the phosphatides the monocytes developed into epithelioid cells, which formed the typical tubercle; with the waxes they fused into foreign body giant cells.

Emphasis has been placed on the action of some fatty acid content in explaining the effects of fats liberated in tissues, but no study has been made to determine the effect soap compounds of various bases may have on inflammatory reactions. Neutralization of rancid olive oil or other oil mixtures by an aqueous solution containing an acid-binding substance is well known commercially.[5] When the soap compound formed is soluble in water, thorough washing with water removes it. If the soap is much less soluble in water, conditions of equilibrium are established at the oil-water interphase which have not yet been thoroughly studied.

In experiments performed in the test tube, oleic acid was shaken with a solution of calcium hydroxide containing phenolsulfonphthalein as indicator. The color of the indicator, which at first showed alkalinity, denoted the shift to acidity, thus demonstrating the entrance of hydrogen

3. Wail, S. S.: Virchows Arch. f. path. Anat. **245**:219, 1923.

3a. Makai, von Quierke and Askanazy, cited by Ansart and Got.[2e]

4. Sabin, F. R.; Doan, C. A., and Forkner, C. E.: Am. Rev. Tuberc. **21**:290, 1930. Smithburn, K. C., and Sabin, F. R.: J. Exper. Med. **61**:771, 1935.

5. Timosuff, V.: Chem. Abstr. **19**:3167, 1925. Bollmann, H.: ibid. **21**:3138, 1927.

ions from the oil phase into the aqueous phase. Presumably, an equivalent amount of base was transferred from the aqueous to the oil phase. This migration of cations into oleic acid may be observed with aqueous solutions of ferric chloride. Oleic acid shaken with such a solution rapidly assumes the red-brown color characteristic of ferric compounds, and the original intensity of color of the aqueous ferric salt solution decreases.

An interchange of base and hydrogen ions between an aqueous solution and oleic acid was demonstrated further by the following experiment:

Oleic acid U. S. P. was shaken with seven changes of distilled water, each time for from one to two hours, to remove any water-soluble material from the acid. Solutions of calcium hydroxide were made from calcium oxide which had been strongly heated to convert any carbonate into oxide. The solution of calcium

TABLE 1.—*Results of Analysis of the Aqueous Layer of the Oleic Acid-Calcium Hydroxide System*

Sample	Oleic Acid, Cc.	Approximate Ratio of Oleic Acid to Ca^{++}	0.01 N Sodium Hydroxide, Cc. (Phenolphthalein)	Normality of Ca^{++} Solution	Remaining Calcium, %	p_H
1	1.5	1.08	11.50 (of 0.01 N hydrochloric acid)	0.00328	15.9	10.54
2	3.0	2.16	0.52	0.00082	4.0	6.90
3	4.5	3.24	0.84	0.00082	4.0	6.60
4	6.0	4.32	0.63	0.00080	3.9	6.49
5	10.0	7.19	0.52	0.00082	4.0	6.25
6	15.0	10.80	0.52	0.00103	4.3	6.24
7	37.5	27.00	1.05	0.00109	5.3	5.88
Control	0	.....	101.90 (of 0.01 N hydrochloric acid)	0.02049		

hydroxide had an alkalinity (or calcium content) such that 100 cc. was equivalent to 1.39 cc. of the washed oleic acid. A solution consisting of 100 cc. of the lime water diluted with an equal volume of distilled water was shaken at room temperature with quantities of washed oleic acid. The mixtures stood overnight, and the oil and the water phase were layered in a separatory funnel, or by special filtration when necessary. The aqueous layer in volumes of 50 cc. each was analyzed for the following factors: acidity to phenolphthalein; presence of organic matter, which reacts with potassium permanganate; content of calcium, and p_H at 30 C. (glass electrode method [6]). The results are stated in table 1.[7]

Analyses of the oil layers for calcium and oleic acid yielded the results shown in table 2.

Pure dry calcium oleate contains 6.63 per cent of calcium. Sample 1 would contain 4.9 per cent of calcium if there were no water. The percentage of calcium decreased from sample 1 to sample 7 because a definite amount of Ca^{++} was available in each mixture and this was introduced into an increasing amount of oleic acid.

6. Hartsuch, Paul J.: J. Infect. Dis., to be published.

7. Mr. Paul J. Hartsuch made the chemical analyses the results of which are given in tables 1 to 4 inclusive.

These chemical reactions were repeated with a more dilute solution of calcium hydroxide (0.00261 normal in Ca^{++} or 0.00244 normal as alkali). The results of analysis of the seven samples are shown in table 3 for the aqueous phase and in table 4 for the oil layer.

TABLE 2.—*Results of Analysis of the Oil Layer of the Oleic Acid-Calcium Hydroxide System*

Sample	Calcium by Weight, %	Oleic Acid by Weight, %	Water (by Difference), %
1	4.34	84.33	11.33
2	1.80	57.74	40.46
3	1.77	84.91	13.32
4	1.49	96.10	2.41
5	0.89	97.11	2.00
6	0.60	97.82	1.58
7	0.24	98.45	1.31

TABLE 3.—*Results of Analysis of the Aqueous Phase with Dilute Solution of Calcium Hydroxide*

Sample	Oleic Acid, Cc.	Approximate Ratio of Oleic Acid to Ca^{++}	0.01 N Sodium Hydroxide, Cc. (Phenolphthalein)	Normality of Ca^{++} Solution	Remaining Calcium, %	p_H
1	0.40	1.16	0.41	0.000394	15.1	7.34
2	0.70	2.04	0.41	0.000406	15.6	6.86
3	1.03	3.00	0.62	0.000370	14.2	6.91
4	1.38	4.02	0.41	0.000538	20.6	6.89
5	2.42	7.04	0.74	0.000574	22.0	6.66
6	3.45	10.00	0.82	0.000398	15.3	6.90
7	8.62	25.20	1.15	0.000718	27.5	6.35
Control	0	.....	12.20 (of 0.01 N hydrochloric acid)	0.00261		

TABLE 4.—*Results of Analysis of the Oil Phase with Dilute Solution of Calcium Hydroxide*

Sample	Calcium, %	Oleic Acid, %	Water, % (by Difference)
1	3.45	67.51	29.04
2	2.03	65.91	32.06
3	1.66	82.55	15.79
4	1.15	96.77	2.08
5	0.68	98.06	1.26
6	0.47	98.37	1.16
7	0.19	99.24	0.57

The analytic results demonstrate that oils containing a fatty acid (oleic) remove base from aqueous solutions in contact. Klotz,[8] in 1905, noted a similar reaction in tissues. He embedded capsules containing fat and fatty acids in animal tissues. After several days the capsules contained calcium soaps, and the calcium content was far in excess of that of normal blood and lymph.

8. Klotz, O.: J. Exper. Med. **7**:633, 1905; **8**:322, 1906.

PROCEDURE OF INVESTIGATION

These observations led to a study of the tissue reactions produced in the lungs of rabbits by intravenous injections of human fat alone and of human fat containing oleic or stearic fatty acid without further chemical treatment and after contact with aqueous alkaline solutions of calcium, strontium and barium hydroxide, respectively.

Human fat was obtained by the warming of finely minced subcutaneous, retroperitoneal and omental fat tissues. The mixtures of human fat and fatty acid were layered over aqueous solutions of calcium, strontium and barium hydroxide, respectively, containing several drops of phenolsulfonphthalein as an indicator. When the color of the indicator in the aqueous solution denoted a shift to acidity, more base was added.

The reactions between the oil and the aqueous phase were completed at 37 C., or at the temperature of boiling water. The rabbits were given an intravenous injection twice each week of from 0.2 to 0.6 cc. of the human fat or human fat mixtures. They were killed from fourteen to twenty-one days after the first injection. Attention was focused in this study on the tissue reactions occurring in the lungs of the rabbits. The type of tissue response varied, as indicated in the following descriptions, according to the base in the soap compound and also, in some experiments, according to the concentration of the oleic or the stearic acid present in the mixture.

TISSUE REACTIONS TO EXPERIMENTAL INJECTIONS OF FAT MIXTURES

Human Fat Alone.—The rabbits in this group lived thirty-six days after the first injection. The pericapillary reactions in the lungs consisted of small masses of well differentiated fibroblastic tissue and a few polymorphonuclear leukocytes and monocytes encapsulating a globule of fat (fig. 1 *A*). About the fat globules were several layers of differentiated fibroblasts. Lesions around the larger blood vessels were proportionately greater than the pericapillary lesions, but of the same general structure. There were a few small foreign body giant cells. Along the edge of the intima of large divisions of the pulmonary artery were thickenings of differentiated fibroblastic tissue. The well organized lesions were composed of fibrous stroma, with several dilated capillaries.

Human Fat (8.5 Cc.) and Oleic Acid (1.5 Cc.).—The pericapillary lesions were larger and revealed a greater reaction of fibroblastic tissue (fig. 1 *B*) than the lesions produced by human fat alone. There were many eosinophilic leukocytes and lymphocytes and some large mononuclear cells. Focal groups of alveoli contained collections of large mononuclear cells. Well organized lesions contained considerable scar tissue.

Human Fat (7.5 Cc.), Oleic Acid (1.5 Cc.) and Stearic Acid (1 Cc.).—The lesions ranged in diameter up to 2 mm. They contained an abundant fibroblastic stroma, with many epithelioid cells and variable numbers of small giant cells (fig. 1 *C*).

Human Fat (9 Cc.) and Stearic Acid (1 Cc.).—Considerable stearic acid crystallized at 37 C. The focal lesions contained a moderate amount of fibroblastic stroma, with many epithelioid cells and some large giant cells, which had inclusions of granular fat material (fig. 1 *D*).

Human Fat (27 Cc.) and Oleic Acid (3 Cc.) Layered Over Calcium Hydroxide.—Around capillaries in the subpleural tissues and the deeper portions of the lungs were exudates of lymphocytes, plasma cells, many eosinophilic leukocytes and a few large mononuclear cells in a scanty fibroblastic stroma (fig. 2*A*). There were similar, but more abundant, cellular exudates around the larger blood

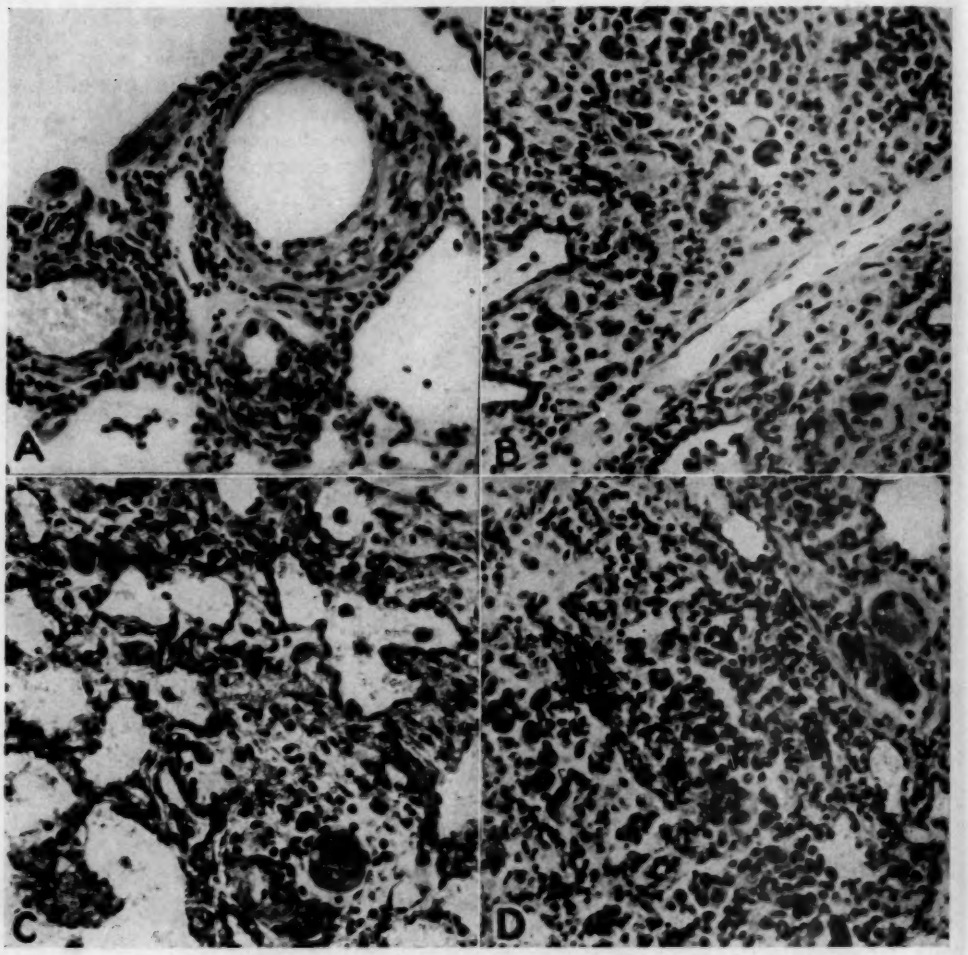

Fig. 1.—Photomicrographs of the tissue reactions produced in the lungs of rabbits with (*A*) human fat; (*B*) human fat and oleic acid in the proportion of 8.5:1.5; (*C*) human fat, oleic and stearic acid in the proportions of 7.5:1.5:1, and (*D*) human fat and stearic acid in the proportion of 9:1.

vessels. The intima of large divisions of the pulmonary artery was markedly infiltrated by the exudates. Little, if any, of the oil material was observed in or about the cells of the exudate. The lumens of a few large blood vessels contained fibroblastic mural thrombi with exudates of plasma cells and leukocytes. In a few alveoli were small groups of large mononuclear cells. The fibroblastic

mural thrombi and intimal thickenings contained no oil material to suggest the causal agent (fig. 2*C*).

Human Fat (36 Cc.), Oleic Acid (3 Cc.) and Stearic Acid (1 Cc.) Layered Over Calcium Hydroxide.—The focal lesions with cellular exudate in the tissues of the lungs of the animals in this group closely resembled the lesions in the

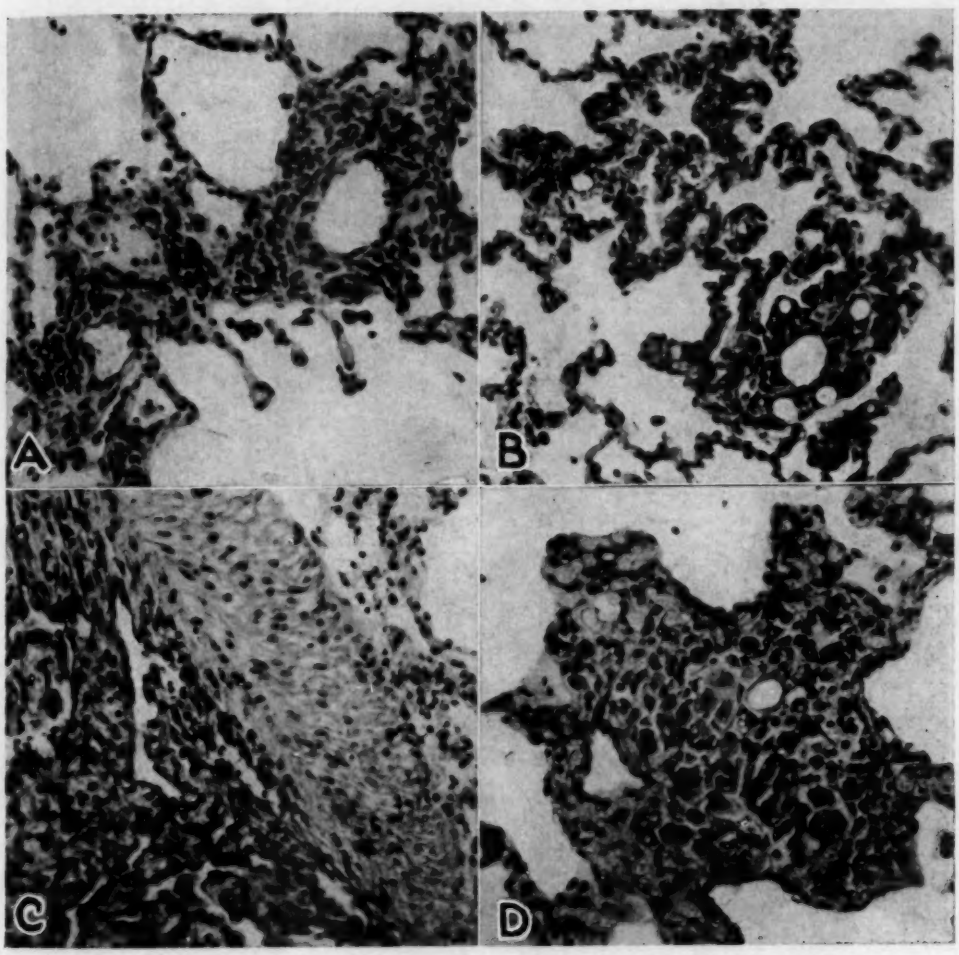

Fig. 2.—Photomicrographs of the tissue reactions produced in the lungs of rabbits with (*A*) human fat containing oleic acid in the proportion of 9:1, neutralized with calcium hydroxide; (*B*) human fat, oleic and stearic acid in the proportion of 9.1:0.3, neutralized with calcium hydroxide, and (*D*) human fat containing oleic acid in the proportion of 9:1, neutralized with strontium hydroxide. *C* illustrates the structure of a thrombus produced with the fat mixture with which changes shown in *B* were obtained.

rabbits of the preceding group. The fibroblastic tissue response seemed greater, and there were a few small giant cells (fig. 2*B*). The medium-sized blood vessels contained fibroblastic mural thrombi, some of which had vacuoles where

oil had been dissolved. There were cellular exudates in the intima and inner portions of the media of the large branches of the pulmonary artery.

Human Fat (29 Cc.) and Stearic Acid (1 Cc.) Layered Over Calcium Hydroxide.—Lesions distributed in foci about the capillaries showed fibroblastic stroma with many large mononuclear cells, some eosinophilic leukocytes and a few lymphocytes and plasma cells. In some of these lesions were several small giant cells. Small and medium divisions of the pulmonary artery contained fibroblastic mural thrombi.

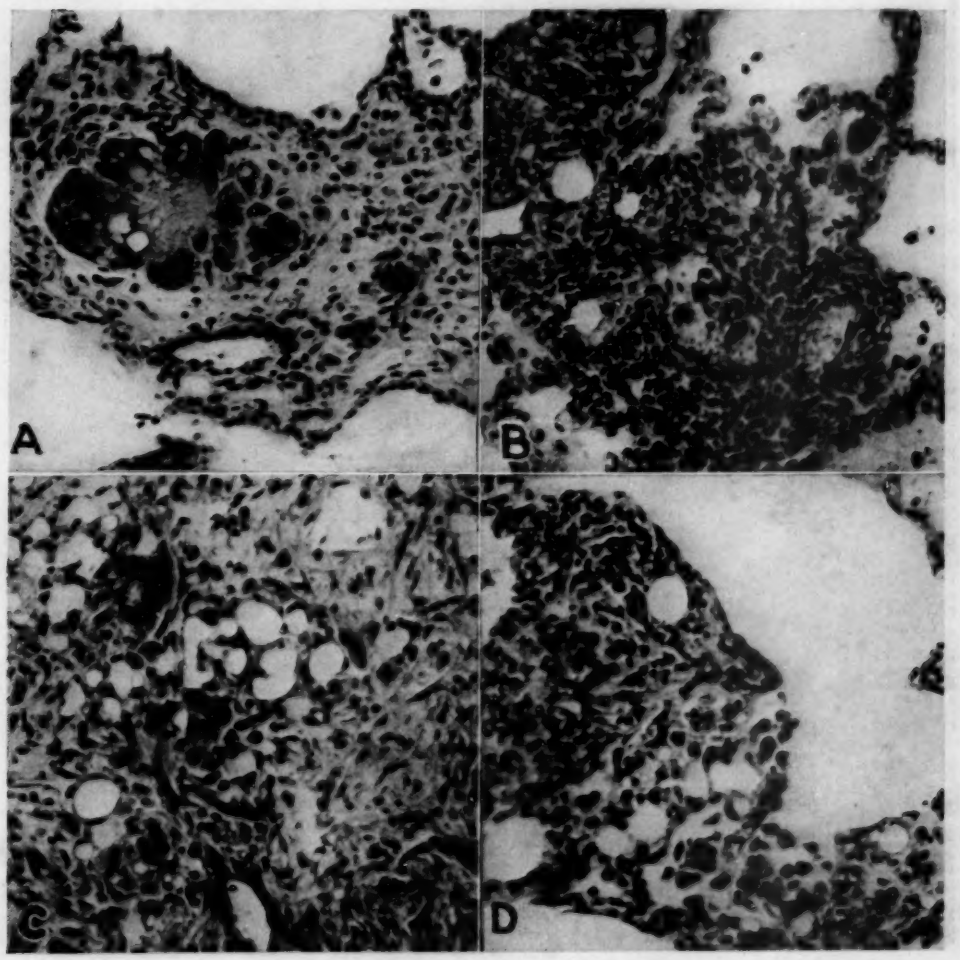

Fig. 3.—Photomicrographs of the tissue reaction produced in the lungs of rabbits with (*A*) human fat containing oleic acid in the proportion of 8.3:1.7, neutralized with strontium hydroxide; (*B*) human fat, oleic and stearic acid in the proportions of 27:2:1, neutralized with strontium hydroxide; (*C*) human fat and oleic acid in the proportion of 9:1, neutralized with barium hydroxide, and (*D*) human fat, oleic and stearic acid in the proportions of 9:1:a trace, neutralized with barium hydroxide.

Human Fat (from 25 to 27 Cc.) and Oleic Acid (from 5 to 3 Cc.) Layered Over Strontium Hydroxide.—The perivascular lesions two weeks after the first injection contained considerable fibroblastic stroma and many large mononuclear (epithelioid cells (fig. 2 *D*). Some of these cells were fused into small giant cells. The mural thrombi in the divisions of the pulmonary artery were composed of similar tissues, some of which contained large giant cells. In older lesions were fibroblastic tissues with large giant cells (fig. 3 *A*), epithelioid cells and a few eosinophilic leukocytes.

Human Fat (27 Cc.), Oleic Acid (2 Cc.) and Stearic Acid (1 Cc.) Layered Over Strontium Hydroxide: Human Fat (29 Cc.) and Stearic Acid (1 Cc.) Layered Over Strontium Hydroxide.—The focal lesions produced with mixtures contained some fibroblastic tissue, epithelioid cells and tissue eosinophilic leukocytes (fig. 3 *B*). The tissue reactions with these mixtures did not seem as marked as those with the mixtures of oleic acid and human fat.

Human Fat (27 Cc.) and Oleic Acid (3 Cc.) Layered Over Barium Hydroxide.—Large subpleural and perivascular lesions contained edematous fibroblastic stroma, with exudates of eosinophilic leukocytes, lymphocytes, plasma cells and epithelioid cells. Masses of epithelioid cells filled the lumens of adjacent alveoli (fig. 3 *C*). Some lesions contained many epithelioid cells and a few giant cells.

Human Fat (27 Cc.), Oleic Acid (3 Cc.) and Stearic Acid (Trace) Layered Over Barium Hydroxide.—The lesions in the lungs produced with this mixture were similar to the lesions produced with the mixture of human fat and oleic acid (fig. 3 *D*). The large divisions of the pulmonary artery contained fibroblastic thrombi.

Human Fat (29.5 Cc.) and Stearic Acid (0.5 Cc.) Layered Over Barium Hydroxide.—The lesions produced in the lung with this mixture were not as large and did not contain as much fibroblastic tissue as the lesions resulting from the other two mixtures of the barium hydroxide series.

COMMENT

The results of the chemical experiments indicate that the introduction into animal tissues of mixtures of human fat and oleic or stearic acid or both affects the tissue until the acidity is neutralized in proportion to the amount of acidity which the fatty acids develop in the tissue fluids through the exchange of ions between the fat and the aqueous medium. On this basis, acidity of sufficient concentration developing about fat in human tissues may cause the initial necrosis which has been described in lesions occurring in lipogranulomatosis. In subcutaneous tissues the neutralization of acidity developing about fat droplets, which takes place by diffusion, doubtless proceeds more slowly than neutralization in the blood, where the globules circulate in an alkaline fluid. According to the experiments on animals, the soap compounds formed in the fat become important in the subsequent reactions of the tissues, depending on their solubility in the aqueous mediums of the tissues, the insoluble compounds remaining in the oil phase. In experiments carried on in the test tube, mixtures of oleic and stearic

acid in human fat were observed to be excellent solvents of calcium and magnesium oleates, palmitates and stearates.

The liquid fats of the body, notably the unsaturated olein, are generally regarded as the solvents for the saturated fats and other lipins, which are solid at body temperature. By hydrolysis the liquid and dissolved fats provide fatty acids which dissolve in the oil droplets the soaps formed with bases from the tissue fluids. The solubilities of the soaps in such oil systems have not been determined, nor is much information available concerning the character of the compounds formed therein—whether they are acid or neutral or both. When the chemical processes continue to form soaps, the compounds probably become neutral because of the alkalinity of the tissue fluids. Olein or other fat reserves of an oil phase are able, by hydrolysis, to provide fatty acids, which in the oil dissolve soaps insoluble in the aqueous phase. Whether the chemical reactions in the oil proceed to an accumulation of neutral soaps or to the formation of soap compounds soluble in the aqueous fluids of the tissues depends on a number of factors, such as the speed and amount of fat hydrolysis and the availability and character of the basic elements in the aqueous fluids of the tissues. When the fat (fatty acid) reserve has been depleted or hydrolysis has ceased and soaps are present in the oil, the tissue reactions about these lipid droplets depend somewhat on the base which has entered the oil system to form a soap compound and also on the character of the fatty acid in the soap.

The apparent barrier to chemical interactions between the liquid fats and the aqueous phase, two immiscible systems, is bridged by fatty acids in the oil phase, the presence of which accomplishes the exchange of hydrogen ions for basic elements of the alkaline aqueous solutions in contact. The probability that these interphase reactions occur in tissues has a basis, of course, in the observations of Klotz. As was demonstrated, in the second set of experiments in this series, even dilute solutions of calcium with concentrations less than that of the blood give up calcium to oleic acid.

The tissue reactions produced by human fat alone, by human fat with a content of oleic or stearic acid or by their soaps (calcium, strontium or barium) progressed from mild inflammation to a marked fibroblastic tissue response with cellular exudates, large monocytes and giant cells. Human fat with a comparatively high content of oleic or stearic acid produced a marked fibroblastic tissue reaction, and the stearic acid mixture, large foreign body giant cells. With the lower concentrations of oleic and stearic acids used in the human fat mixtures, the calcium soap compounds caused an exudation of leukocytes and a moderate fibroblastic tissue response, while the strontium and barium compounds stimulated a marked fibroblastic reaction and epithelioid and giant cells. Many of the fibroblastic thrombi in the large and

medium-sized divisions of the pulmonary arteries contained no trace of the lipid materials which had caused their formation. This circumstance indicates some of the difficulties encountered in attempts to determine the etiology of organized thrombi in the lungs in man.

A variable factor not controlled in the experiments described was the degree of neutralization of the fatty acid in the oil phase, and no attempt was made in this study to correlate the quantity of fatty acids added to human fat with the character of the tissue response. Perhaps concentrations of oleic acid in human fat mixtures greater than the concentrations used may produce, after neutralization with calcium hydroxide, tissue reactions similar to those noted after neutralization with strontium or barium hydroxide. Or the effects of low concentrations in oil systems treated with barium hydroxide approach those of high concentrations in systems treated with calcium hydroxide.

SUMMARY

The fatty acids of oil systems in contact with alkaline aqueous solutions exchange hydrogen ions for the basic ions dissolved in the aqueous fluid.

Fatty acids in such oil systems are solvents for certain soaps insoluble in aqueous solutions.

Human fat containing fatty acids abstracts basic ions from aqueous liquids in contact, and the soaps so formed are important in determining the subsequent tissue reactions.

When an oil contains dissolved fatty acid, the exchange of hydrogen and basic ions at the oil-water interphase is an important link in the chemical reactions of the two immiscible systems.

Human fat with a comparatively high content of oleic or stearic acid produced in the lungs of rabbits a marked fibroblastic tissue reaction, and the stearic acid mixture, large foreign body giant cells.

Human fat containing low concentrations of oleic and stearic acids neutralized with calcium hydroxide stimulated leukocytic exudates and a moderate fibroblastic tissue response. After neutralization with strontium or barium hydroxide this mixture stimulated a marked reaction of fibroblastic tissue and epithelioid and giant cells.

THE SHWARTZMAN PHENOMENON IN THE KIDNEYS OF RABBITS

OBSERVATIONS ON EFFECTS OF INTRAVENOUS ADMINISTRATION OF BACTERIAL FILTRATES

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The phenomenon of local cutaneous reactivity to bacterial filtrates, described by Shwartzman,[1] has been produced in the testes, intestine, lymphatic glands and thymus of rabbits and guinea-pigs and in liposarcoma of the guinea-pig by Gratia and Linz,[2] in the knee joints of rabbits by Moritz and Morley [3] and in the stomach of rabbits by Karsner, Ecker and Jackson.[4] In these instances the organs were prepared by a direct intraparenchymal injection of the bacterial filtrate. After a suitable interval, usually twenty-four hours, the reacting or provocative dose was administered intravenously, and the phenomenon was obtained four hours later. Direct preparation of an organ (kidney or ear) by way of its vascular supply was reported by Shwartzman,[5] and the phenomenon was then elicited by the subsequent intravenous injection of the reacting factors. Recently, Gratia and Linz, Apitz [6] and Gronchi [7] studied the effect of repeated intravenous injections of bacterial filtrates. They observed certain pathologic changes in the internal organs of the animals and expressed the belief that these represent a generalized phenomenon analogous to the local Shwartzman phenomenon.

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* Emanuel Libman Fellow. Part of this work was done under the tenure of the George Blumenthal Jr. Fellowship in Pathology.

1. Shwartzman, G.: Proc. Soc. Exper. Biol. & Med. **25**:560, 1928; J. Exper. Med. **48**:247, 1928.

2. Gratia, A., and Linz, R.: Ann. Inst. Pasteur **49**:131, 1932.

3. Moritz, A. R., and Morley, J. D.: Proc. Soc. Exper. Biol. & Med. **29**: 321, 1931.

4. Karsner, H. T.; Ecker, E. E., and Jackson, E. L.: Proc. Soc. Exper. Biol. & Med. **29**:319, 1931.

5. Shwartzman, G.: (*a*) J. Exper. Med. **51**:571, 1930; (*b*) **62**:621, 1935.

6. Apitz, K.: Virchows Arch. f. path. Anat. **293**:1, 1934; J. Immunol. **29**: 255, 1935.

7. Gronchi, V.: Boll. d. Soc. ital. di biol. sper. **9**:1032, 1934.

My purpose in the present study was to determine the generalized effects of the intravenous injection of bacterial filtrates in rabbits. A number of factors were investigated. These included the effects of a single injection of varying doses of bacterial filtrate, two injections of filtrate with variations in the doses and the interval of time between the injections, the simultaneous elicitation of the local Shwartzman phenomenon and the intravenous injection of bacterial filtrate and the substitution of the second intravenous injection of bacterial filtrate by the antigen-antibody combination.

EXPERIMENTAL PROCEDURE

Rabbits were used in all the experiments. Meningococcus and typhoid bacillus filtrates were employed. They were prepared according to the method described by Shwartzman [8] and were capable of eliciting the local Shwartzman phenomenon. Their reacting potency was determined [9] and expressed in reacting units. Dilutions of the filtrates were made with physiologic solution of sodium chloride so that, for intravenous use, the desired number of reacting units was delivered in 1 cc. of solution per kilogram of body weight. The total amount of culture filtrate injected varied from 0.005 to 2 cc. (from 20 to 1,000 reacting units). Preparation of the skin, either preceding or simultaneous with the first intravenous injection, was performed in a number of animals. Such animals uniformly received an intradermal injection of 0.25 cc. of solution. This quantity contained the desired dilution of the preparatory factors.

Autopsy was performed on the rabbits soon after death or after the animals were killed at varying intervals by the injection of 10 cc. of air into the marginal vein of the ear. This method was found to be most desirable since prolonged severe convulsions were avoided and traumatic hemorrhage was minimal. The tissues were fixed in a dilute solution of formaldehyde U. S. P. (1:5). Staining with hematoxylin and eosin, sudan, the Van Gieson method and the Weigert methods for fibrin and elastic tissue and bacterial staining were performed. The heart, liver, spleen, kidneys and lungs of nearly all the animals were examined, and the adrenals, intestine, pancreas, lymph nodes, bone marrow, thymus and genitalia were sectioned in a number of instances.

The experiments were divided into the following three groups:

Group 1: Effect of a single intravenous injection of bacterial filtrate.

Group 2: Effect of two intravenous injections of bacterial filtrate.

Group 3: Effect of a single injection of bacterial filtrate in animals previously sensitized to normal horse serum, followed by reinjection of normal horse serum.

The experimental procedures and the summaries of the protocols are given in the accompanying tables.

The pathologic alterations in the internal organs were nearly identical in the three groups. The differences between the groups consisted in the frequency of involvement of the organs, the number of organs affected in an individual animal and the extent of the changes in a given organ. Hence, the morphologic alterations in individual organs will be described, and the essential differences between the three groups will then be analyzed.

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8. Shwartzman, G.: Proc. Soc. Exper. Biol. & Med. **26**:843, 1929; J. Infect. Dis. **45**:232, 1929.

9. Shwartzman, G.: J. Exper. Med. **52**:781, 1930.

Ten normal rabbits from the same stock as that from which the experimental animals were taken were killed, and the internal organs were examined grossly and microscopically for purposes of control.

OBSERVATIONS ON VARIOUS ORGANS

Heart.—In animals which died at varying intervals after the intravenous injection of the bacterial filtrate, dilatation of the right auricle and ventricle was frequently shown. However, this was not always associated with concomitant histologic changes. In a number of instances the anterior surface of both ventricles presented scattered gray flecks and marked vascular congestion.

Microscopically, the alterations consisted of three types, namely, severe cloudy swelling, with waxy degeneration of the muscle fibers; focal necroses, with or without calcification, and interstitial cellular infiltration, with or without focal necroses. All three types were often present concurrently.

The extent of the cardiac involvement varied from minute foci of waxy change of the muscle fibers to extensive areas of interstitial infiltration and necrosis with calcification. The changes were observed in both ventricles, but predominantly in the right. The interstitial infiltration consisted of large, monocytic elements, lymphocytes, polymorphonuclear leukocytes and macrophages. Occasionally, the subendocardial tissues, particularly of the right auricle and ventricle, were infiltrated, and the intima of the pulmonary artery and the aorta was similarly invaded. This was seen chiefly in animals which had previously been sensitized to normal horse serum.

Proliferation of the endothelium of the aorta, mitral valve and ventricular wall was observed in several instances. This occurred only in animals previously sensitized to horse serum. Lesions of the coronary vessels were not seen.

The hearts of the ten normal control animals showed varying degrees of waxy change of the muscle fibers and interstitial infiltration. Focal necroses were uncommon. These lesions corresponded with the changes reported in the literature as spontaneous myocarditis.[10] The changes just described clearly indicate that the intravenous injection of bacterial filtrate or normal horse serum or both is productive of greater degenerative and inflammatory changes than those which occur spontaneously. However, the lesions were inconstant and variable and could not be related specifically either to the amount of filtrate injected or to the length of time the animal lived after the injection. Animals sensitized to normal horse serum presented more frequent and more extensive degenerative changes.

Liver.—The frequent occurrence of coccidiosis in stock rabbits required extreme caution in the interpretation of morphologic changes in this organ. In nearly all the animals some degree of coccidial infection was shown, which expressed itself in gross and microscopic alterations. The liver was often studded with gray-white, firm nodules. The organ was firmer and smaller than normal and offered increased resistance to the knife in a number of instances. Scattered gray-red irregular flecks, from about 0.5 to 1 mm. in diameter, were frequently seen on the surface of the liver of rabbits in the experimental group. These were associated with focal necroses and venous thrombi, to be described later.

The histologic changes in this organ, exclusive of the lesions attributable to coccidial infection, consisted of two types, namely, focal necroses and venous thrombi. The necroses of the liver cells varied in size from small foci, either in the central or the middle portion of the lobule, to large areas involving an

10. Miller, C. P.: J. Exper. Med. **40**:543, 1924.

entire lobule and portions of the adjacent lobules. The necrotic cells were often surrounded by polymorphonuclear leukocytes and a few macrophages. Although similar small foci of necrosis were seen in animals used as controls which were suffering from coccidiosis, this lesion was more extensive in the experimental animals and hence was looked on as a direct effect of the injection of bacterial

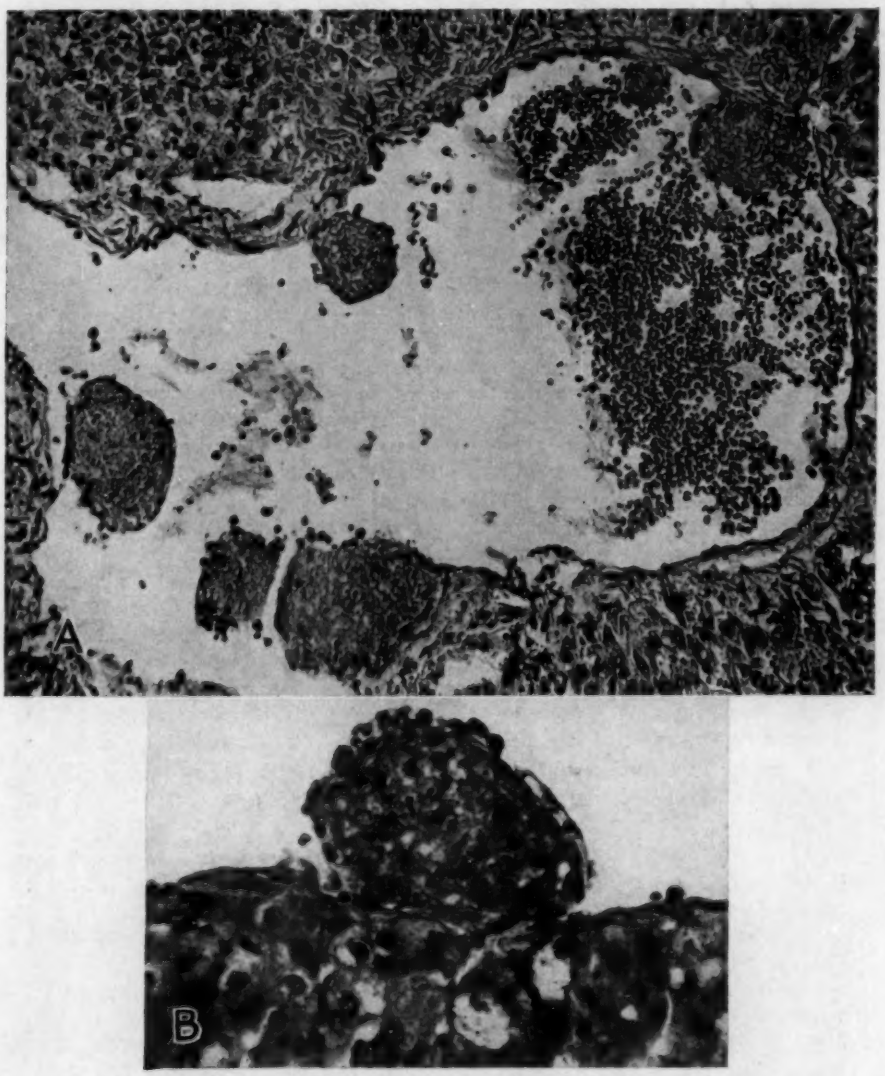

Fig. 1 (rabbit 601 [table 3]).—*A* is a low power view of a large hepatic vein with many parietal thrombi; hematoxylin and eosin stain. *B* is a high power view (hematoxylin and eosin stain) of a portion of the section shown in *A*, illustrating the structure of a thrombus. The wall of the vein at the site of attachment of the thrombus is unaltered.

filtrate. Extensive necrosis was often accompanied with a greater degree of venous thrombosis.

The thrombi were observed chiefly in the central, sublobular or large hepatic veins, occasionally in the sinusoids in the vicinity of the central vein and more rarely in small branches of the portal vein. The arteries were entirely free from thrombi or other changes. There was great variation in the extent of venous thrombosis. While in some instances only isolated central or sublobular venous thrombi were noted, in others there was almost complete involvement of all the central and sublobular veins in several representative histologic sections. The thrombi showed marked variation in size and little variation in appearance. They were round or elongated and rested on the vascular endothelium. Often a large sublobular vein contained a number of parietal thrombi spaced at intervals (fig. 1*A*). Massive thrombi, filling almost the entire lumen of a large tributary of the hepatic vein, were seen in two instances. Occlusion of the lumen of a central vein by a large plug was seen at times.

The thrombi consisted of spongy or compact, amorphous, eosinophilic masses or clumps, with enmeshed erythrocytes and leukocytes (fig. 1*B*). The cells at times showed advanced degenerative changes, so that only shadows of erythrocytes or nuclear remnants were observed among the eosinophilic masses. The thrombi contained varying numbers of cells. The spongy appearance was often striking. This gave rise to the impression that in the precipitation of these masses varying numbers of blood cells were embodied. With the Weigert stain for fibrin the thrombi were observed to contain irregular clumps of fibrin, and, rarely, strands. The amount of fibrin varied but was usually small, the main mass consisting of an amorphous substance.

Serial sections of veins containing thrombi revealed no endothelial changes. Similarly, the venous walls, either at the site of attachment of a thrombus or elsewhere, showed no alteration. Occasionally, subendothelial round cell infiltrations were seen in branches of the portal vein and, less commonly, in sublobular veins. These cellular collections pushed the endothelium forward and jutted into the lumen of the vessel. However, since this lesion was also seen in animals used as controls, particularly in instances in which there was severe infiltration of the peripheral connective tissue, it was attributed to chronic infection due to coccidiosis. Organization or alterations that could be interpreted as evidences of beginning organization of the thrombi were not noted. Animals which lived seventy-two hours or longer often showed thrombi which were fragmented and small.

Lungs.—In rabbits which were killed, no gross morphologic changes were shown in the lungs. Petechial hemorrhages were noted on the pleural surface of the lungs of animals which were found dead.

Microscopically, the outstanding changes in the lungs consisted of edema, hemorrhage and venous thrombosis. Not infrequently, foci of acute or chronic pneumonia were seen; these also occurred in animals used as controls. The edema and hemorrhage varied in extent. Edema was observed only in animals which died. The hemorrhages were often multiple but never large or extensive. The venous thombi were identical with the thrombi described in the liver (fig. 2*A*). Variations in the size and extent of the thrombi were similarly noted. Occasionally, thrombi were seen in the arteries, although the veins and capillaries were chiefly affected. Organization of the thrombi was not observed.

Spleen.—The effects of preexisting infection were taken into consideration in an evaluation of the morphologic changes in the spleen. This organ varied mark-

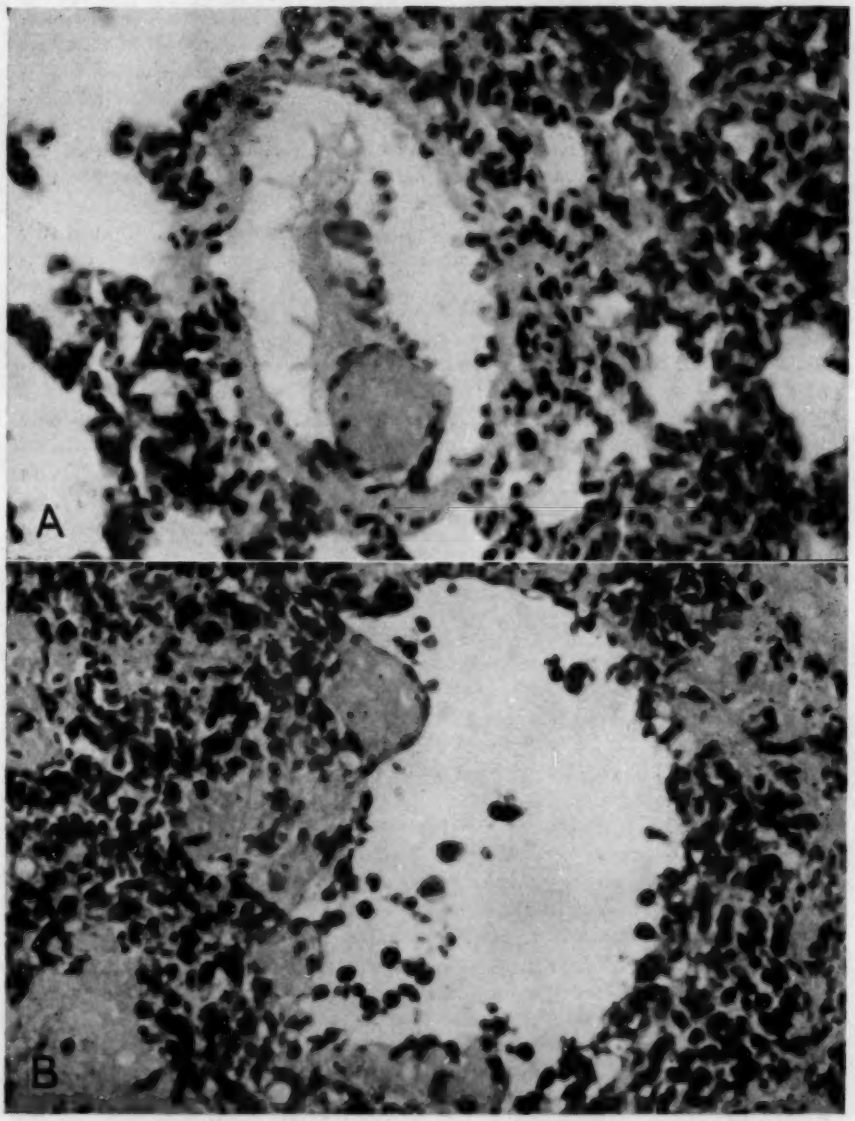

Fig. 2.—*A* (rabbit 58 [table 2]) shows a parietal venous thrombus in the lung, and *B* (rabbit 706 [table 3]), parietal venous thrombi in the spleen and thrombi also filling the surrounding splenic sinuses; hematoxylin and eosin stain.

edly in size both in the experimental animals and in those used as controls. An enlarged and firm spleen, often with gray-red irregular flecks on the surface, usually presented lesions which could be attributed to the effect of the intravenously injected filtrate.

The histologic alterations of the spleen consisted of focal necrosis and thrombosis of the splenic sinuses, the branches of the splenic vein and, rarely, arterioles of the malpighian corpuscles. Variations in cellular constituents, sinusoidal congestion and the presence of iron in the cords and sinuses occurred in both experimental and control animals and thus were not considered to be due to the effect of the bacterial filtrate. However, the presence of foci of proliferation of the reticulum cells in the spleen of rabbits in the experimental series suggested that this may be due to the effect of the injected bacterial filtrate.

Focal necroses were observed in both the malpighian corpuscles and the splenic pulp. The foci in the pulp were often subcapsular and sharply circumscribed, resembling infarcts.

The thrombi in the branches of the splenic vein and central arterioles of the malpighian corpuscles resembled the thrombi described in the liver and lungs (fig. 2 *B*). The thrombotic masses in the sinusoids appeared as ill defined, eosinophilic material in which much nuclear débris was present. Often every sinusoid appeared to be filled with these masses; less frequently, the thrombi were seen only in foci. They did not possess the specific, round form noted in the thrombi of the liver or lungs but filled the entire sinus, to which they conformed. With the Weigert stain for fibrin these thrombotic masses showed irregular coarse clumps and, less commonly, strands of fibrin. Organized thrombi were not observed.

Kidneys.—As in other organs, it was necessary to exclude spontaneous lesions in an evaluation of the effects of the injected bacterial filtrate. Spontaneous renal lesions were recognized grossly by diffuse cortical scarring. Such scars, on histologic examination, showed focal interstitial round cell infiltration, increase in connective tissue and glomerular and tubular atrophy. These lesions were seen both in experimental animals and in those used as controls and were identical with the lesions described in the literature.[11]

The pathologic changes resulting from injection of the bacterial filtrate consisted of three types, namely, diffusely distributed punctate hemorrhages, focal cortical necroses, often with punctate hemorrhages, and diffuse cortical necrosis, acompanied by extensive hemorrhages. The lesions were limited to the cortex (fig. 3). Kidneys which did not present gross morphologic alterations were usually normal on microscopic examination, except for slight cloudy swelling of the tubules and rare thrombi of the veins or glomerular capillaries.

Kidneys showing diffusely distributed hemorrhages, from the size of a pinpoint to that of a pinhead, presented on microscopic examination discrete interstitial hemorrhages in the cortex. The intertubular and glomerular capillaries were dilated and congested. Not infrequently extravasated erythrocytes were present in Bowman's space. Thrombi of the glomerular capillaries were present in varying degrees. The thrombi, which consisted of amorphous eosinophilic masses, almost filled the glomerular capillaries. With the Weigert stain for fibrin they appeared deep blue, but no strands of fibrin were discernible. The larger renal vessels in these instances were unaltered.

Focal cortical necroses appeared grossly as scattered irregular gray-red flecks on the surface, from about 0.5 to 1 mm. in diameter, accompanied frequently by

11. Bell, E. T., and Hartzell, T. B.: J. Infect. Dis. **24**:628, 1919. Ophüls, W.: Proc. Soc. Exper. Biol. & Med. **8**:75, 1910-1911.

hemorrhages the size of a pinhead. Microscopically, there were focal areas of tubular necrosis, sharply defined from the surrounding intact tissue. Most commonly the convoluted tubules were involved. In a number of instances tubular necrosis occurred alone, without other alterations. However, this lesion was observed more commonly in association with hemorrhages, as already described, and with foci of thrombosis of the glomerular capillaries and of glomerular hemorrhage (fig. 4*A*). In instances of the last-mentioned lesions it was possible to demonstrate the presence of necrosis and thrombosis of branches of the interlobular arteries corresponding to the focal necrotic areas. Serial sections demon-

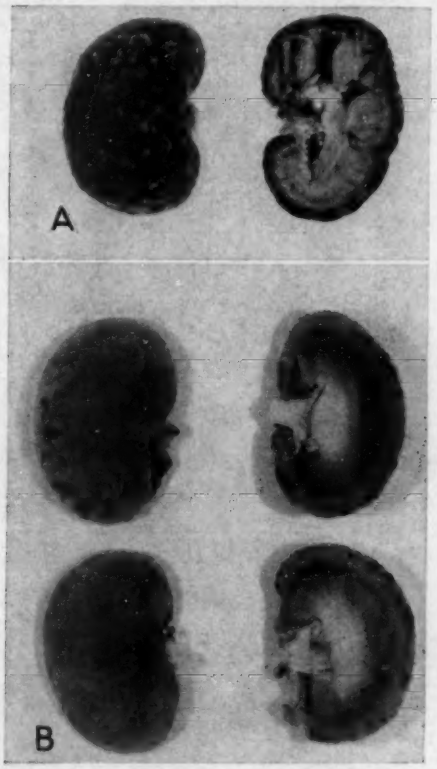

Fig. 3 (rabbits 491 and 601 [table 3]).—Gross appearance of the kidneys, showing focal and diffuse cortical necrosis. The process does not involve the medulla.

strated that only a short segment of the vessel was involved. The entire wall was necrotic, with extravasation of erythrocytes and filling of the lumen with a thrombus that contained clumps of fibrin. Infiltrations of polymorphonuclear leukocytes were seen about the necrotic portion of the vessel. At times the necrosis extended into the afferent arterioles of the glomeruli.

Grossly, the most striking renal lesion observed was that of diffuse cortical necrosis. The surface was irregular and covered with numerous elevated, hemorrhagic areas, alternating with depressed gray areas. The process ended abruptly

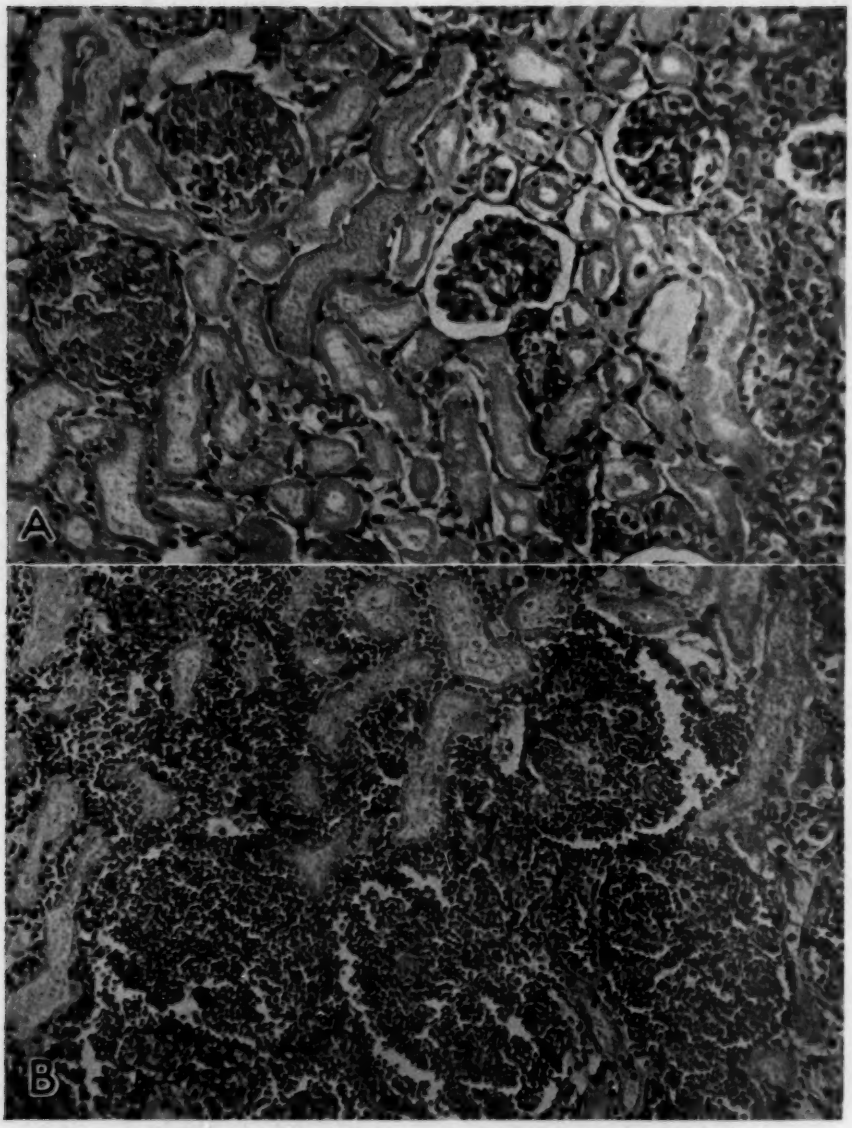

Fig. 4.—*A* (rabbit 601 [table 3]) shows an area of focal tubular necrosis, with capillary thrombosis of the adjacent glomeruli, and *B* (rabbit 491 [table 3]), hemorrhagic necrosis of the renal cortex; hematoxylin and eosin stain.

at the medulla. Histologically, there were diffuse tubular necrosis, interstitial and glomerular hemorrhage and thrombosis of the glomerular capillaries. Many glomeruli were replaced by hemorrhages which filled the entire capsular space and did not permit the recognition of the capillary loops (fig. 4*B*). The tubules showed various stages of necrosis. There was necrosis of the interlobular arteries, as already described, with hemorrhage around and into the wall of the vessels and perivascular leukocytic infiltration. Only small residual areas of uninvolved renal tissue were noted. These were demarcated from the necrotic areas by a dense zone of leukocytic infiltration. Not infrequently, glomeruli in these uninvolved zones showed focal capillary thrombosis and extravasation of erythrocytes into the capsular spaces.

With the stain for elastic tissue the necrotic vessels showed complete disruption of the elastic fibers. In the thrombi only clumps of fibrin were seen; strands of fibrin could not be demonstrated.

Endothelial alterations of the vessels or glomerular capillaries were not noted, except of course in the instances in which necrosis had involved the structure.

As the animals presenting renal lesions were killed within twenty-four hours after the second intravenous injection of bacterial filtrate, the further course of the vascular alterations was not observed.

Adrenals.—Aside from the occasional observation of isolated parietal venous thrombi, the essential lesion consisted of a sharply demarcated area of necrosis involving chiefly the cortex and at times the adjacent medulla. Grossly, the adrenal was enlarged and presented a circumscribed gray-red zone, readily distinguishable from the normal glandular tissue. The periphery of this zone was marked off from the normal tissue by a narrow hemorrhagic ring. The necrotic area varied in size from one seen only on microscopic examination tc one involving almost the entire gland. The lesion was always unilateral. Microscopically, the necrotic area was demarcated from the uninvolved tissue by a zone of leukocytes. Within the necrotic area the cellular structures were no longer recognized. Only small quantities of fibrin were observed chiefly at the periphery. Involvement of the arteries could not be demonstrated, even with serial sections. Foci of hemorrhage were observed in the cortex in a number of instances. These were not associated with thrombi or other vascular changes.

Bone Marrow.—The lesions in the marrow consisted of focal necrosis and capillary and venous thrombi. There was no distinct association of the two lesions. The necrosis resembled the type seen in the adrenal. It consisted of a circular area of cellular débris within which little original structure of the marrow was discerned. This was sharply defined from the adjacent normal marrow. Vascular involvement corresponding to the area of necrosis could not be demonstrated.

The capillary and venous thrombi were identical with corresponding lesions in the other organs. Foci of hemorrhage were seen occasionally. Corresponding vascular changes were not noted. There was no notable alteration of the cellular components of the bone marrow.

Other Organs.—The thymus, mesenteric lymph nodes, omentum, striated muscle, testes, uterus, ovaries and small and large intestines were examined in a number of instances. The only lesions observed were occasional areas of necrosis of the lymphatic follicles of the appendix, similar to the necrosis occurring in the malpighian corpuscles of the spleen. Venous thrombi were seen in the appendix in one instance.

OBSERVATIONS ON THE THREE GROUPS

Group 1.—The protocols for animals in this group are summarized in table 1. The rabbits were divided into three series. One series of animals received a

TABLE 1.—*Data on the Group of Rabbits Receiving a Single Intravenous Injection of Bacterial Filtrates* *

Animal	Skin-Preparatory Dose Bacterial Filtrate (0.25 Cc.), Dilution	Interval Before Intravenous Injection of Filtrate, Hours	Intravenous Dose of Bacterial Filtrate, Reacting Units	Time of Survival, Hours	Cutaneous Reaction	Changes in Organs									Comments
						Heart	Lungs	Liver	Spleen	Kidneys	Adrenals	Pancreas†	Bone Marrow†	Intestines†	
853	.....	..	Men. 50	K 28	..	..	..	..	..	..	..	..	..	..	
813	.....	..	Men. 50	K 28	..	..	..	..	+	..	N	..	..	..	
884	.....	..	Men. 50	K 28	..	..	..	..	..	..	..	..	+	..	
158	.....	..	Typh. 100	D 4	..	..	+	..	..	..	..	..	..	..	
138	.. ..	..	Typh. 100	D 4	..	..	+	..	..	..	..	..	..	..	
30	....	..	Typh. 150	K 48	..	..	..	..	..	..	..	..	..	..	
160	.....	..	Typh. 150	K 48	..	..	..	..	..	..	..	..	..	..	
848	.....	..	Men. 150	K 28	..	..	..	..	..	..	..	..	..	..	
855	.....	..	Men. 150	K 28	..	..	..	..	+	..	..	..	..	..	
866	.....	..	Men. 150	K 28	..	..	..	..	+	..	..	..	..	..	
893	....	..	Men. 250	D 4	..	..	..	+	+	..	..	..	+	..	
822	.....	..	Men. 250	D 4	..	..	+	..	+	..	..	..	..	+	
477	.....	..	Men. 250	D 4	..	..	..	+	+	..	..	..	+	..	
154	. .....	..	Men. 80	D 6	..	..	..	..	..	..	..	..	..	..	These animals all received 1 cc. of normal horse serum intravenously six days prior to injection of the bacterial filtrate
574	.....	..	Men. 100	D 4	..	..	+	+	+	..	..	..	..	..	
502	.....	..	Men. 100	D 4	..	..	+	+	..	..	..	..	..	..	
514	.....	..	Men. 100	D 6	..	..	+	..	+	..	..	..	..	..	
578	.....	..	Men. 100	D 6	..	..	+	+	+	..	..	..	..	..	
638	Men. 1:150	24	Men. 25	K 24	0	..	..	..	..	..	..	..	..	..	
684	Typh. 1:150	24	Men. 25	K 24	±	..	..	..	..	..	..	..	..	..	
197	Men. 1:10	24	Men. 25	K 24	+	..	..	..	..	..	..	..	..	..	
104	Men. 1:10	24	Men. 25	K 24	+	..	..	+	+	..	..	..	+	..	
107	Men. 1:10	24	Men. 25	K 24	+	..	+	+	+	..	N	..	..	..	
111	Typh. 1:10	24	Men. 25	K 24	+	..	..	..	..	..	..	..	..	..	
157	Typh. 1:10	24	Men. 25	K 24	+	..	..	..	..	..	..	..	..	..	
167	Typh. 1:10	24	Men. 25	K 24	±	..	..	..	+	..	..	..	..	..	
562	Men. 1:2	24	Men. 100	D 4	+	..	+	+	+	..	..	..	..	..	

* The abbreviations used in this table and in the accompanying tables are identical. Men. indicates the meningococcus filtrate; typh., typhoid bacillus filtrate; K, that the animal was killed, and D, that the animal died. In the column headed "Cutaneous Reaction" 0 indicates a negative reaction, and x, that the cutaneous reaction was not read because of postmortem discoloration. A + sign in the columns for the various organs indicates that venous thrombi were present, and in the column "Kidney" the mark denotes that one of the various types of lesions described for that organ was observed. N in the columns "Adrenals" and "Bone Marrow" denotes the presence of circumscribed necrosis, as described for these organs.

† The pancreas, bone marrow and intestine were examined in six, eighteen and twenty animals, respectively. The remaining organs were examined in all instances.

TABLE 2.—*Data on Groups of Rabbits Receiving Two Intravenous Injections of Bacterial Filtrates*

Animal	First Intravenous Dose of Bacterial Filtrate Reacting Units	Interval, Hours	Second Intravenous Dose, Reacting Units	Time of Survival, Hours	Changes in Organs									Comments
					Heart	Lungs	Liver	Spleen	Kidneys	Adrenals	Pancreas*	Bone Marrow*	Intestines*	
274	Men. 50	24	Men. 50	K 24	..	..	..	..	..	..	..	..	..	
293	Men. 50	24	Men. 50	K 24	..	..	..	..	..	..	..	..	..	
226	Typh. 50	24	Typh. 50	K 24	..	..	..	..	..	..	..	..	..	
240	Men. 80	24	Men. 25	K 24	..	..	+	..	..	..	..	..	..	
58	Men. 100	24	Men. 50	K 72	..	+	+	..	..	..	..	..	..	
59	Men. 100	24	Men. 50	K 72	..	..	+	..	..	..	..	..	..	
85	Men. 100	24	Men. 50	K 120	..	..	..	..	..	..	..	..	..	
656	Men. 100	24	Men. 100	K 24	..	+	+	+	+	..	..	..	..	
641	Men. 100	24	Men. 100	K 24	..	..	..	..	..	..	..	..	..	
647	Men. 100	24	Men. 100	D 4	..	..	..	+	..	..	..	..	..	
74	Men. 100	24	Men. 100	D 1	..	+	..	+	..	..	..	..	..	
92	Typh. 100	24	Typh. 500	D 3	..	..	..	..	..	..	..	..	..	
77	Typh. 100	24	Typh. 500	D 3	..	+	+	+	..	..	..	..	..	
125	Typh. 350	24	Typh. 350	K 24	..	+	+	..	..	..	..	..	..	The typhoid bacillus filtrate used for these animals was partially neutralized by homologous antitoxic horse serum. The dose stated in the table represents the strength in reacting units of the filtrate after partial neutralization
176	Typh. 350	24	Typh. 350	K 72	..	+	..	..	..	..	..	..	..	
146	Typh. 350	24	Typh. 350	K 144	..	..	..	..	..	..	..	..	..	
196	Typh. 350	24	Typh. 350	K 72	..	..	+	..	..	..	..	..	..	
218	Typh. 500	24	Typh. 500	K 50	..	..	+	..	..	..	..	..	..	
203	Typh. 500	24	Typh. 500	K 31	..	+	+	..	..	..	..	..	..	
294	Typh. 500	6	Typh. 500	K 24	..	+	..	+	..	..	..	..	..	
276	Typh. 500	6	Typh. 500	K 24	..	+	+	..	+	..	..	..	..	
239	Typh. 500	6	Typh. 500	D 4	..	+	..	+	..	..	..	..	..	
229	Typh. 500	6	Typh. 500	K 55	..	..	..	..	..	..	..	..	..	
189	Men. 100	6	Men. 100	D 4	..	..	..	..	..	..	..	..	..	
299	Men. 100	6	Men. 100	D 4	..	..	..	+	..	..	..	..	..	
168	Men. 100	6	Men. 100	K 31	..	..	+	..	..	..	..	..	..	
213	Men. 100	48	Men. 100	D 4	..	..	+	+	..	..	..	..	..	
285	Men. 100	48	Men. 100	D 4	..	..	+	..	..	..	..	..	..	
233	Men. 100	48	Men. 100	K 24	..	+	+	+	..	..	..	..	..	

* The pancreas, bone marrow and intestine were examined in five, two and seven animals, respectively. The remaining organs were examined in all instances.

TABLE 3.—*Data on Groups of Rabbits with Skin Preparation Receiving Two Intravenous Injections of Bacterial Filtrate*

Animal	Skin-Preparatory Dose of Bacterial Filtrate (0.25 Cc.), Dilution	Interval Before First Intravenous Injection	First Intravenous Dose of Bacterial Filtrate, Reacting Units	Interval, Hours	Second Intravenous Dose, Reacting Units	Time of Survival, Hours	Cutaneous Reaction	Changes in Organs									Comments
								Heart	Lungs	Liver	Spleen	Kidneys	Adrenals	Pancreas*	Bone Marrow*	Intestine*	
491	Men. 1:25	Immediately	Men. 25	24	Men. 100	K 24	+	..	+	+	+	+	..	..	..	..	
673	Men. 1:2	Immediately	Men. 100	24	Men. 100	K 24	+	..	+	+	+	+	..	..	..	..	
601	Men. 1:2	Immediately	Men. 100	24	Men. 100	K 24	+	..	+	+	+	+	..	..	..	..	
747	Men. 1:2	Immediately	Men. 100	24	Men. 100	D 4	+	..	+	+	+	..	..	..	..	..	
706	Men. 1:2	Immediately	Men. 100	24	Men. 100	K 24	+	..	..	+	+	+	N	+	..	..	
719	Men. 1:2	Immediately	Men. 100	24	Men. 100	K 48	+	..	..	+	..	..	..	..	N	..	
124	Typh. undilute	Immediately	Typh. 100	24	Typh. 100	D 4	x	..	+	..	+	..	..	..	..	..	
130	Typh. undilute	Immediately	Typh. 100	24	Typh. 100	D 4	x	..	+	+	+	..	..	..	..	..	
144	Typh. undilute	Immediately	Typh. 100	24	Typh. 100	D 4	x	..	+	..	+	..	..	..	..	..	
767	Typh. undilute	Immediately	Typh. 25	24	Typh. 50	D 4	+	..	+	+	+	..	..	..	..	..	
241	Typh. undilute	Immediately	Typh. 50	24	Typh. 300	D 0	x	..	..	..	+	..	..	+	..	..	
295	Typh. undilute	Immediately	Typh. 50	24	Typh. 300	D 4	x	..	+	..	+	..	..	..	..	..	
42	Typh. undilute	Immediately	Typh. 100	24	Typh. 500	D 3	x	..	..	..	..	..	..	..	..	..	
26	Typh. undilute	Immediately	Typh. 100	24	Typh. 500	D 3	+	..	+	+	+	..	..	..	..	..	
238	Typh. undilute	Immediately	Typh. 500	24	Typh. 500	D 4	+	..	+	+	+	..	N	..	..	..	The typhoid bacillus filtrate used in this group was partially neutralized
222	Typh. undilute	Immediately	Typh. 500	24	Typh. 500	D 4	+	..	+	+	+	+	..	..	..	..	
201	Typh. undilute	Immediately	Typh. 500	24	Typh. 500	D 4	x	..	..	..	..	..	..	..	..	..	
205	Typh. undilute	Immediately	Typh. 500	24	Typh. 500	D 4	x	..	+	..	+	..	..	..	..	..	
346	Typh. undilute	Immediately	Typh. 500	24	Typh. 500	K 24	+	..	+	+	+	..	..	..	..	..	
266	Men. 1:2	Immediately	Men. 100	24	Typh. 400	D 18	+	..	..	+	..	..	..	..	+	..	
332	Men. 1:2	Immediately	Men. 100	24	Typh. 400	D 48	+	..	+	+	+	..	..	..	..	..	
265	Men. 1:2	Immediately	Men. 100	24	Typh. 400	K 144	+	..	..	..	..	..	..	..	..	..	
451	Men. 1:2	Immediately	Men. 100	24	Typh. 600	K 48	+	..	+	+	..	..	..	..	..	..	
489	Men. 1:2	Immediately	Men. 100	24	Typh. 600	K 96	0	..	..	..	+	..	N	..	..	..	
459	Men. 1:2	Immediately	Typh. 600	24	Men. 100	K 96	0	..	..	..	..	..	N	..	..	..	
148	Men. 1:2	6 hours	Men. 80	24	Men. 100	K 24	+	..	..	+	+	..	..	..	..	..	
166	Men. 1:2	6 hours	Men. 80	24	Men. 100	D 4	+	..	..	+	+	..	..	..	..	..	
186	Men. 1:2	6 hours	Men. 80	24	Men. 100	K 55	+	..	..	+	+	..	..	..	..	..	
248	Men. 1:2	6 hours	Men. 200	24	Men. 100	D 4	+	..	..	+	..	..	..	..	..	..	
261	Men. 1:2	6 hours	Men. 200	24	Men. 100	D 4	0	..	..	..	..	..	..	..	..	..	
224	Men. 1:2	24 hours	Men. 80	24	Men. 100	D 4	+	..	..	+	+	..	N	..	..	..	
297	Men. 1:2	24 hours	Men. 160	24	Men. 100	K 31	+	..	+	+	+	..	..	..	..	..	
193	Men. 1:2	24 horus	Men. 160	24	Men. 100	D 4	+	..	..	..	..	..	..	..	..	..	
525	Men. 1:2	24 hours	Men. 100	24	Men. 100	D 4	+	..	+	+	+	..	..	..	..	..	
536	Men. 1:2	24 hours	Men. 100	24	Men. 100	K 24	+	..	+	+	+	..	+	..	..	..	

* The pancreas, bone marrow and intestine were examined in seven, six and fourteen animals, respectively. The remaining organs were examined in all instances.

single intravenous injection of bacterial filtrate; a second series was sensitized to normal horse serum by the intravenous injection of 1 cc. per kilogram of body weight and received, six days later, a single intravenous injection of bacterial filtrate, and a third series was given an intradermal injection of bacterial filtrate (skin preparation) twenty-four hours prior to the intravenous injection of bacterial filtrate. In seventeen of the entire group of twenty-seven animals, or in 63 per cent, venous thrombi were shown in one or several organs. The lungs, liver and spleen were involved in nine, eight and thirteen instances, respectively. Renal lesions did not occur. Necrosis of the adrenals was observed in two instances. Degenerative changes in the heart, liver and spleen were present in a number of instances.

Group 2.—The animals were divided into two series. One, consisting of twenty-nine rabbits, received two intravenous injections of bacterial filtrate six, twenty-four or forty-eight hours apart. The second series, consisting of thirty-five rabbits, received an intradermal injection of bacterial filtrate twenty-four hours, six hours or immediately prior to the first intravenous injection, and the second intravenous injection was given twenty-four hours later.

The summaries of the protocols for the first series are given in table 2. In twenty, or 69 per cent, of the twenty-nine animals venous thrombi were shown in one or more organs. The lungs, liver and spleen were affected in eleven, fourteen and nine instances, respectively. Renal alterations were observed in two animals. Necrosis of the adrenals was not observed. Degenerative changes in the heart, liver and spleen were noted somewhat more frequently in these rabbits than in the animals of group 1.

The protocols for the animals in the second series are summarized in table 3.

In twenty-nine, or 82.8 per cent, of the thirty-five rabbits venous thrombi were shown in one or more organs. The lungs, liver and spleen were involved in nineteen, twenty-three and twenty-five instances, respectively. Renal lesions occurred in five instances, and necrosis of the adrenals was observed in five.

The incidence of positive cutaneous reactions, exclusive of the reactions which were not read because of postmortem discoloration of the skin site, conformed with that noted by Shwartzman—approximately 90 per cent. Only three animals responded with negative cutaneous reactions. Venous thrombi were observed but once—in the spleen of one of the three animals. It is not possible to conclude on the basis of this small series whether or not failure of elicitation of the local Shwarztman phenomenon can be considered to be an indicator of the resistance of the animal to the generalized effect of intravenously administered filtrate.

Degenerative changes in the heart, liver and spleen occurred with greater frequency in this than in the first series.

Group 3.—My purpose in this experiment was to determine the effect of substitution of the antigen-antibody combination for the second intravenous injection of bacterial filtrate as a reacting factor. The procedure followed was analogous to that employed by Shwartzman [12] in obtaining the local phenomenon. He prepared the skin of rabbits previously sensitized to horse serum by an intradermal injection of bacterial filtrate and twenty-four hours later administered an intravenous injection of normal horse serum. The local phenomenon appeared within an hour. Shwartzman also demonstrated that other antigen-antibody combinations are capable of acting as reacting factors. However, the antigen-antibody combination did not prepare the skin for the phenomenon.

12. Shwartzman, G.: Science **76**:127, 1932.

TABLE 4.—*Data on the Group of Rabbits Sensitized to Normal Horse Serum Receiving an Intravenous Injection of Bacterial Filtrate*

Animal	No. of Doses of Normal Horse Serum Injected Intravenously (1 Cc. per Kg. of Body Weight at 6 Day Intervals)	Interval Before Intravenous Injection of Bacterial Filtrate, Days	Intravenous Dose of Bacterial Filtrate, Reacting Units	Interval Before Intravenous Injection of Antigen (1 Cc. Normal Horse Serum per Kg. of Body Weight)	Time of Survival, Hours	Changes in Organs									Comments
						Heart	Lungs	Liver	Spleen	Kidneys	Adrenals	Pancreas*	Bone Marrow*	Intestines*	
16	1	..	.....	6 days	K 48	..	..	..	..	..	..	..	..	..	Control
4	1	..	.....	6 days	K 48	..	..	..	..	..	..	..	..	..	Control
7	1	..	.....	6 days	K 72	..	..	..	..	..	..	..	..	..	Control
117	1	6	Men. 80	24 hours	D 4	..	+	..	..	..	..	..	..	..	
170	1	6	Men. 80	24 hours	D 4	..	+	..	..	..	..	..	..	..	
131	1	6	Men. 80	24 hours	D 4	..	+	..	..	..	..	..	..	..	
173	1	6	Men. 80	24 hours	K 24	..	..	..	..	..	..	..	..	..	
166	1	6	Men. 100	24 hours	K 24	..	+	+	+	..	..	..	..	..	
167	1	6	Men. 100	24 hours	K 72	..	+	..	..	..	N	..	..	..	
120	3	6	Men. 100	24 hours	K 48	..	..	..	..	..	..	..	..	..	
319	2	6	Men. 100	24 hours	K 48	..	..	..	..	..	..	..	..	..	
564	2	6	Men. 100	24 hours	K 24	..	+	..	..	..	..	..	N	..	
197	1	6	Men. 80	24 hours	K 31	..	..	..	..	..	..	..	..	..	Skin preparation with meningococcus filtrate 1:2; reaction +
183	1	6	Men. 80	24 hours	K 50	..	..	+	..	..	..	..	..	..	
393	1	6	Men. 100	6 hours	K 48	..	..	..	..	..	..	..	..	..	
685	1	6	Men. 100	6 hours	K 48	..	..	..	..	..	..	..	..	..	
507	1	6	Men. 100	6 hours	D 4	..	+	+	+	..	..	..	..	..	

* The pancreas, bone marrow and intestine were examined in two, one and seven animals, respectively. The remaining organs were examined in all instances.

In the present experiment fourteen rabbits were sensitized by the intravenous injection of 1 cc. of normal horse serum per kilogram of body weight. Six days later the animals were given an intravenous injection of bacterial filtrate. This was followed six or twenty-four hours later by a second injection of normal horse serum. Two of the rabbits also received an intradermal injection of bacterial filtrate twenty-four hours prior to the intravenous administration of bacterial filtrate, and the local phenomenon was obtained in both instances. Three additional rabbits each received two intravenous injections of normal horse serum six days apart for purposes of control.

In eight of the fourteen animals venous thrombi were presented in one or more organs. The lungs, liver and spleen were involved in seven, three and two instances, respectively. Necrosis of the adrenals occurred once. The degenerative changes in the heart were most striking in this group and were far in excess of the cardiac changes observed in nonsensitized animals which received injections of bacterial filtrate. The three animals used as controls presented only moderately severe degenerative changes in the heart, and venous thrombi were not noted.

COMMENT

Degenerative changes and venous thrombi in the internal organs, exclusive of the kidneys, were obtained with either one or two injections of bacterial filtrate. The number of animals showing venous thrombi is nearly the same in both instances for the three groups, (tables 1, 2 and 4), or 63, 69 and 57 per cent, respectively. However, the rabbits which received skin preparation together with two intravenous injections of bacterial filtrate showed a higher incidence of involvement, 82.8 per cent (table 3). Similarly, the incidence and extent of involvement of the organs were higher in this series.

Koplik [13] has shown that lymph nodes far removed from the prepared skin site show hemorrhages and thrombi after the appearance of the local Shwartzman phenomenon. It is not unlikely that some of the filtrate passes from the prepared skin site into the lymphatic system and thence into the general circulation. The intradermal dose, in terms of reacting units, is usually very high (a dilution of meningococcus filtrate of 1:2, used for skin preparation, may represent as high as 1,000 reacting units), so that the intravenous absorption of even a small quantity may represent a dose as large as that usually given intravenously in the present experiments. It appears, therefore, that the higher incidence of venous thrombi when skin preparation accompanied two intravenous injections of bacterial filtrate may be accounted for by the intravenous absorption of additional filtrate from the prepared skin site. A comparison of the effect of large doses with that of small doses of filtrate in the absence of skin preparation indicates that the larger the quantity of filtrate which reaches the general circulation the higher is the incidence of involvement of both animals and organs (tables 1 and 2).

13. Koplik, L. H.: Personal communication to the author.

Differences in the efficacy of the filtrates employed, namely, meningococcus and typhoid bacillus filtrates, were not noted. The resultant lesions were nearly identical, provided that the dose in terms of reacting units was the same.

The earliest period at which venous thrombi were observed after the intravenous injection of the filtrate was four hours. Whether or not this lesion may be obtained sooner was not determined.

The production of venous thrombi in the internal organs of rabbits, identical with the lesions described by Apitz and with those observed in the present experiments, was reported by Kusama [14] in 1913, following the injection of vaccines of typhoid bacilli, dysentery bacilli and staphylococci. It is possible that the active factor in the vaccines responsible for the thrombotic lesions was identical with the bacterial filtrates employed in the present experiments. Bacterial filtrates are heat resistant, and the preparation of vaccines does not alter their potency appreciably. Identical venous thrombi were obtained by Siegmund [15] after the intravenous injection of living cultures of typhoid bacilli, colon bacilli and staphylococci.

Organization of the thrombi was not observed in the present experiments. In animals which were allowed to live three days or longer a diminishing frequency of thrombi was usually shown. The fragmentary appearance and the small size of the thrombi, when present in animals which survived three days or longer, suggest that the thrombotic masses tend to be broken up. These observations, together with the absence of endothelial alterations, either at the site of lodgment of the thrombi or elsewhere, support the theory that the thrombi may disappear without leaving any trace. Kusama likewise stated that the thrombotic masses tend to be reabsorbed later. On the other hand, Apitz and also Siegmund described organization of the venous thrombi. Subendothelial collections of monocytic cells, which strikingly resembled the intimal granulomas described by Siegmund, were seen in the portal and sublobular veins in a number of instances in the present study. However, since these were likewise seen in animals used as controls and were always associated with marked cellular infiltration of the periportal connective tissue, they were considered to be coincident with chronic coccidial infection.

The origin of the thrombi remains obscure. The absence of endothelial reaction points to some primary effect of the bacterial filtrate on elements in the circulating blood. The preponderance of the thrombi in the veins and capillaries of the lungs, liver and spleen (the bone marrow was not examined in a sufficiently large series), in which the

14. Kusama, S.: Beitr. z. path. Anat. u. z. allg. Path. **55**:459, 1913.
15. Siegmund, H.: Verhandl. d. deutsch. path. Gesellsch. **20**:260, 1925.

circulation is comparatively slow, indicates that this factor may play a rôle in their formation. Whether or not endothelial "hyperactivity" without evident morphologic alterations is also of account in the formation of such thrombi, as Dietrich [16] held, cannot be determined. Hematologic studies were not made.

Siegmund called attention to the presence of venous thrombi and intimal granulomas in chronic infection in man. He compared them with the lesions obtained experimentally and suggested that a similar pathogenesis may be operative. Bacteria-free thrombi have been observed in the vessels of the heart, liver and kidneys in a number of cases of acute infection in which necropsy was done as a routine at the Mount Sinai Hospital. It may thus be assumed that in infection in man the causative organism elaborates a toxin identical with that obtained from culture filtrates and that this may be responsible for the lesions.

The venous thrombi and degenerative changes in the internal organs are probably the result of a primary toxicity of the bacterial filtrate; since they are observed with either one or more injections of the filtrate, they cannot be directly related to the Shwartzman phenomenon. However, the renal lesions which were observed only after the intravenous injection of two doses of bacterial filtrate twenty-four hours apart are in the nature of a Shwartzman phenomenon. This was first pointed out by Apitz in his studies on what he termed the generalized Shwartzman phenomenon. Gratia and Linz observed hemorrhages in the internal organs after the intravenous injection of repeated doses of bacterial filtrate and considered these changes to be a manifestation of a generalized phenomenon, since they were unable to obtain them with one dose. However, Bordet [17] observed that the intravenous injection of a single large dose of colon bacillus filtrate, concentrated with acetic acid, produced hemorrhages in the lungs of rabbits and guinea-pigs. He ascribed these lesions to the primary hemorrhagic property of the bacterial toxins. Although Gratia and Linz observed no effects after a single intravenous injection, even though the dose was as large as the sum of two injections given twenty-four hours apart, they did not report microscopic examination of the tissues. As indicated in the description of the organs in the present experiments, histologic changes were often present without concomitant gross alterations. Gronchi's view that hemorrhage and necrosis of the adrenals are

16. Dietrich, A.: Thrombose: Ihre Grundlagen und ihre Bedeutung, in Aschoff, L., and others: Pathologie und Klinik in Einzeldarstellung, Berlin, Julius Springer, 1932, vol. 4.

17. Bordet, P.: Compt. rend. Soc. de biol. **114**:574, 1933.

manifestations of a generalized phenomenon cannot be accepted, since these lesions were observed in the present experiments after the intravenous injection of only a single dose of filtrate.

Recently Apitz extended the criteria for the recognition of the generalized phenomenon to include, in addition to the renal lesions, either death of the animal within forty-eight hours after the second injection or considerable hemorrhage in the internal organs. Single lethal doses, he stated, did not produce renal changes or hemorrhages. These criteria are both open to question. In the present study, death of the animal was observed to follow a single injection with the same frequency as that after two injections. Large doses of filtrate, particularly typhoid bacillus filtrate, would lead to death of the animal more often than a similar quantity given in two divided doses. Partial neutralization of the typhoid bacillus filtrate with the homologous antitoxic horse serum permitted the use of much larger doses of the filtrate, with an appreciable reduction in the mortality rate. This observation was first made by Shwartzman [18] in the production of hemorrhagic necrosis and regression of mouse sarcoma by the intravenous injection of bacterial filtrate. Partial neutralization of the filtrate reduces the lethal effect to a proportionately greater extent than the factors responsible for the degenerative changes or thrombi in the internal organs of the rabbit. Likewise, hemorrhages were never striking in the present experiments and occurred only in animals which died. Animals which were killed by the injection of air into the marginal vein of the ear did not show more than occasional petechial hemorrhages.

Consideration of the renal lesions as a Shwartzman phenomenon takes into account the fact that both the preparation and the reaction of the organ are obtained by way of the general circulation. The possibility of preparing tissues by the vascular route was demonstrated by Shwartzman, who obtained the phenomenon in the kidneys of rabbits after preparation by injection of the bacterial filtrate into the renal arteries. Recently Shwartzman [5b] was able to prepare the ear of the rabbit for the local phenomenon by injecting the filtrate into the marginal vein and clamping the ear so that venous obstruction resulted for five minutes. However, preparation occurred only when the vascular permeability was altered, either by the local application of heat or by the administration of the preparatory dose admixed with testicular extract.

The optimum interval between injections for the production of the renal changes was twenty-four hours. Animals which received two intravenous injections either six or forty-eight hours apart did not

18. Shwartzman, G.: Science 82:201, 1935.

show changes in the kidney. It is possible that with the use of doses much larger than those employed the necessary interval between injections may be reduced.

Lesions of the kidney closely resembling the changes described in the present study have been produced by the intravenous injection of concentrated bacterial filtrates which are apparently not capable of eliciting the local Shwartzman phenomenon, namely staphylococcus toxins (Rigdon, Joyner and Ricketts,[19] Von Glahn and Weld[20] and others).[21] The renal changes were obtained in rabbits, dogs and cats after the intravenous injection of one or more doses of the toxin. Venous thrombi in the lungs, liver or spleen were not described. An outstanding feature, in addition to the renal lesions, was the presence of severe hemorrhage into the serous cavities and organs (Rigdon).[22]

Cortical renal necrosis, similar to the type described in the present study, has been observed in infection in animals and man. Röhrer[23] described this lesion in spontaneous hog cholera and was able to produce the lesion by the experimental injection of the specific virus in hogs for the purpose of producing immunity. He described hemorrhages and focal tubular necrosis in the kidneys as well and stated that these changes occurred more frequently than cortical necrosis, especially if secondary invaders (such as Bacillus suipestifer) were also present. In man cortical necrosis has been observed in cases of diphtheria, scarlet fever, grip and malaria and incidentally in cases of tonsillitis and other infections (von Zalka[24]). The association of the lesion with infection in man and animals and its resemblance to experimentally produced renal alterations suggests that a similar pathogenesis may be operative. It is possible that, as regards the production of renal necrosis, injected viruses are similar in their behavior to bacterial toxins, since, as has been shown by Gratia and Linz and Koplik,[25] the local Shwartzman phenomenon can be produced by preparation with virus and injection of either virus or bacterial toxin as the reacting factor.

The etiology of cortical renal necrosis occasionally seen in eclampsia is obscure. Jeddeloh[26] described thrombosis of the glomerular capil-

19. Rigdon, R. H.; Joyner, A. L., and Ricketts, E. T.: Am. J. Path. **10**:425, 1934.

20. Von Glahn, W. C., and Weld, J. T.: J. Exper. Med. **61**:1, 1935.

21. The question as to whether the staphylococcus toxins contain the Shwartzman active principles remains open. According to Gratia and Linz, staphylococcus filtrates are inactive. On the other hand, Gross (Klin. Wchnschr. **11**:1473, 1932) was able to obtain the typical local Shwartzman phenomenon with culture filtrates of strains which did not yield the primary necrotic lesions in the skin of rabbits.

22. Rigdon, R. H.: Arch. Path. **20**:201, 1935.

23. Röhrer, H.: Virchows Arch. f. path. Anat. **284**:203, 1932.

24. von Zalka, E.: Virchows Arch. f. path. Anat. **290**:53, 1933.

25. Koplik, L. H.: Am. J. Path. **11**:842, 1935.

26. zu Jeddeloh, B.: Virchows Arch. f. path. Anat. **286**:389, 1932.

laries and necrosis of the afferent arterioles in two patients after miscarriage. Since no organisms were demonstrable, he ascribed these changes to bacterial toxins and related them to the group of cortical necroses occurring in eclampsia. In this connection it is interesting to note that Apitz obtained renal lesions in pregnant rabbits after the intravenous injection of only a single dose of bacterial filtrate. This author maintained that pregnancy per se acted as a preparatory factor, so that after only a single dose of toxin lesions were obtained similar to the changes produced in nonpregnant rabbits for which two doses were required.

The similarity of the pathologic changes induced in rabbits by the intravenous administration of bacterial filtrates, as already described, to the changes observed in man suggests that this experimental method may throw further light on the pathogenesis of human infection. However, conditions in man analogous to those produced experimentally by the intravenous introduction of large quantities of bacterial toxins probably occur only under limited circumstances, such as overwhelming infection with powerful toxin-producing organisms. Even in these instances such pathologic changes are observed only infrequently. Certain factors, such as partial immunity of the host, variations in the potency of the toxin and toxin-producing qualities of the invading organism and vascular permeability to the toxins, must be taken into consideration in such experimental studies. Investigations are now under way to study the effects of several of these factors on the response of rabbits to the prolonged intravenous introduction of bacterial toxins.

SUMMARY AND CONCLUSIONS

The intravenous injection of either one or two doses of bacterial filtrate resulted in the appearance of venous thrombi and degenerative changes in the internal organs of rabbits.

Renal lesions, consisting of thrombosis of the glomerular capillaries, focal tubular necrosis and focal or diffuse cortical necrosis, with necrotizing arteritis of the interlobular vessels, were observed in a number of instances. These occurred only when two intravenous injections of bacterial filtrate were given twenty-four hours apart, and they are considered to represent the Shwartzman phenomenon.

The similarity of the pathologic changes induced in rabbits by the intravenous injection of bacterial filtrates to the changes observed in spontaneous and experimental infections in animals and in association with infection in man suggests that a similar pathogenesis may be operative.

ACQUIRED RESISTANCE TO TUBERCULOSIS

WITH INVESTIGATIONS INTO THE VALIDITY OF RANKE'S CLASSIFICATION

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The problem of immunity in tuberculosis has come to no satisfactory conclusion despite decades of controversy. The protagonists of the theory of acquired resistance (Roemer,[1] Krause[2] and Baldwin and Gardner[3]) have been opposed by those who have minimized the importance of acquired in favor of native (species or constitutional) resistance (Neufeld[4]) or who have doubted even that the protection given by an infection continues after the lesion becomes quiescent (Bruno Lange,[5] Lydtin[6]). Myers and his school[7] have regarded preallergic native resistance not only as paramount but even as well-nigh perfect and have ascribed to the hypersensitivity ("allergy") arising from the primary infection the responsibility for subsequent fatal issues.

Doubtless the complex of immunity in tuberculosis is the resultant of many different factors, most important of which are the native resistance, the acquired resistance, the amount of infection and the nutritional state of the infected person. The relative importance of these different factors and their several mechanisms[8] will not be discussed; but evidence will be presented favoring the assumption that a person does acquire some resistance in the course of a primary infection and that the changed status of cells or of body fluids is sufficient to alter favorably (for the existence of the person) the reaction of the body to reinfection.

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1. Roemer, P. H.: Ztschr. f. Infektionskr. **6**:393, 1909.
2. Krause, A. K.: Am. Rev. Tuberc. **14**:271, 1926.
3. Baldwin, E. R., and Gardner, L. U.: Am. Rev. Tuberc. **5**:429, 1921.
4. Neufeld, F.: Beitr. z. Klin. d. Tuberk. **70**:280, 1928.
5. Lange, Bruno: Beitr. z. Klin. d. Tuberk. **75**:191, 1930.
6. Lydtin, K.: Beitr. z. Klin. d. Tuberk. **75**:189, 1930.
7. Myers, J. Arthur: Journal-Lancet **53**:457, 1933. Johnson, Wathena Myers, and Myers, J. Arthur: Am. Rev. Tuberc. **28**:381, 1933. Stewart, Chester A.: Am. J. Dis. Child. **43**:803, 1932.
8. Rich, A. R., and McKee, C. M.: Bull. Johns Hopkins Hosp. **54**:277, 1934. Rich, A. R., and McCordock, H. A.: ibid. **44**:273, 1929.

It has generally been accepted that a certain degree of resistance is acquired during the course of a primary infection. The observations which led to this belief were incorporated by Ranke[9] in his classification of tuberculosis. He assumed that there are three stages of the disease: (1) the primary focus, (2) the spreading of the bacilli and (3) tertiary phthisis of an organ or of an organ system. Stage 1 is characterized by the presence of one or more sharply defined foci of the disease in the parenchyma of an organ accessible to the exterior of the body and also in the lymph nodes directly draining that area. In stage 2 the individual foci are diminished to the point of extinction, and the spread of the bacilli may take place by any route: lymph tracts, lymph nodes, blood stream and natural avenues, such as serous surfaces and bronchi. The manifestations of this stage may range from clinically imperceptible to miliary tuberculosis. Recovery and subsequent reinfection, whether endogenous or exogenous, lead to stage 3, isolated chronic disease of an organ or of an organ system. Lymph nodes show only abortive tubercles, and morphologic evidence of hematogenous distribution is unusual. Nevertheless, the destruction of an organ or of an organ system may be complete because of advance along preestablished avenues of communication in organs especially predisposed by their anatomic structure. Advance by establishment of contiguous tubercles also is noted.

Essential to this classification is the concept of a blockade which, developing in the course of a primary infection, localizes all subsequent lesions. This will be subsequently spoken of as the lymphatic or the hematic blockade. Ranke's opinions on this point have, however, been disputed. We therefore tested them, by personal investigations organized for this purpose, with regard to all cases of active tuberculosis in which autopsy was performed in the Cleveland City Hospital from June 1934 to July 1935. Other aspects of Ranke's classification, such as the question whether stages 1 and 2 are sequential (a point concerning which there is considerable ambiguity in Ranke's publications) or to a degree concomitant, will not be discussed.

There were eighty-seven cases, six of which were not included in this study because the findings were incomplete or controversial. A dilute solution of formaldehyde U. S. P. (1:10) was injected into the lungs in situ by way of either the pulmonary artery or the trachea. After having been left for forty-eight hours in a crock containing a solution of formaldehyde, the lungs were cut with a long, broad knife into coronal sections. A special blank form was prepared for recording the gross and microscopic descriptions of the organs, the essential purpose being not only to tabulate the presence of tuberculous lesions, active or

9. Ranke, K. E.: Ausgewählte Schriften zur Tuberkulosepathologie, in Pagel, W., and Pagel, M.: Die Tuberkulose und ihre Grenzgebiete in Einzeldarstellungen, Berlin, Julius Springer, 1928, vol. 6.

obsolete, in any part of the body but to register their character and when possible to trace the pathogenic relations. Practically all the autopsies were performed with one or both of us present; all were done under the direction of one of us (H. S. R.), and all the forms were filled out by us with at least the lungs and their appendages at hand. Microscopic sections were taken from the lungs, the parenchyma as well as the lymph nodes, the liver, the spleen, the kidneys and the mesenteric nodes and on occasion from some other organ. The sections were stained by the usual hematoxylin and eosin method and, when indicated, by special stains, such as the Verhoeff or the Ziehl-Neelsen stain, and were studied by both of us. At the end of the form a final opinion concerning the type of tuberculous disease and the efficiency of the blockade was appended. The statistics were based subsequently on these opinions.

It is obvious that some grouping of the cases was necessary to permit statistical treatment. The classification which was used for this study was as follows:

A. Reinfection:

1. Subacute pulmonary tuberculosis. Conglomerate or pneumonic lesions are present. The former are soft, with evidences of much perifocal reaction and with little or no fibrosis. Pneumonia is greatly in evidence. Liquefaction necrosis is commonly present in the center of each type of lesion. The cavities have soft, shaggy walls with little trabeculation. On microscopic examination the walls are shown to consist chiefly of areas of compression atelectasis and pneumonia, although some granulation tissue may be seen. Microscopic examination is required for the exact classification, because atelectasis and other changes may resemble fibrosis grossly. Fibrosis is slight or absent. Sequestration cavities are common; these are roughly circular, and their walls consist of shaggy necrotic tissue. The pleura is frequently involved, and ruptures into the pleural space may occur.

2. Chronic ulcerative pulmonary tuberculosis. Conglomerate lesions predominate, although toward the end of the course pneumonia may be present. The conglomerate lesions tend to be discrete, with little or no evidence of any perifocal reaction. There is ample evidence of a proliferative reaction, and frequently the lesions are walled off by a firm barrier of proliferation or even of granulation tissue. The cavities are irregular, multilocular and trabeculated and have firm walls, which consist in whole or in part of connective tissue associated with evidence of tuberculous inflammation. Cavitation is by the slow process of ulceration or, as it may more properly be called, attrition. Fibrosis and obliteration of the pleura are common. These processes are found chiefly in the apical and dorsal portions of the lungs; the base may be uninvolved even to the end. Bronchiogenic distribution to the opposite lung is frequent. Toward the end of the course the subacute phase may intervene, but, nevertheless, the case is placed in this group.

3. Chronic fibrous pulmonary tuberculosis. Conglomerate lesions predominate, and pneumonia is rarely present except as a terminal event. The conglomerate lesions are discrete and often remarkably firm, and there is practically no evidence of perifocal reaction. The lesions stand out like nodules in an emphysematous lung. They are surrounded by firm, dense connective tissue, which extends as a stellate scar into the surrounding lung tissue. There is often a striking absence of exudation. Hyalinization of the connective tissue is common. Liquefaction or even caseation is infrequent and when present is usually distinctly walled off by connective tissue ("throttled reaction"). When cavities are present they are usually located in the apex or in the subapical region. They are irregular and multiloculated and may be large. Usually each cavity has a clean wall, which consists of extremely dense and often acellular hyalinized connective tissue in which tubercles are seen. Smaller cavities are frequently formed by dilated bronchi. Tuberculous bronchiectasis and tuberculous bronchitis and peribronchitis are frequent in this group. Bronchiogenic distribution often leads to bronchial disease in other parts of the lung. The pleura is thick and often densely adherent to the wall of the chest and to the diaphragm. This type of tuberculosis is often associated with pneumoconiosis or collapse therapy and is present also in older persons.

4. Apical pulmonary tuberculosis, with conglomerate lesions. This is actually the early stage of one of the first three groups. Conglomerate lesions that are proliferative or, more unusually, exudative are situated in the apical and subapical regions. They are in general fairly well delimited, but there may be some perifocal pneumonia. Frequently several different stages of tubercle formation can be made out, such as old hyalinized tubercles, fresh proliferative tubercles and older proliferative tubercles with a central caseated area. Not infrequently rupture into moderate-sized apical bronchi and early bronchiogenic distribution can be made out.

5. Extrapulmonary tuberculosis. In this group are included all cases of tuberculosis of any organ or organ system outside the lung, such as the genito-urinary system, the adrenal glands and the bones.

6. Reactivated primary complex. There is a "healed" primary infection, with reactivation of the primary focus or primary node.

B. Primary infection:

1. Active progressive primary infection. In this group the primary lesion as well as the lymph nodes draining the primary lesion shows active tuberculosis. The size of the primary lesion is inconsequential. It may measure not more than 5 mm., or it may occupy an entire lobe of a lung. The usual terminal event is miliary tuberculosis.

2. Active healing primary infection. In this group there is evidence that the primary focus and most of the lesions in the nodes are

healing. The patient dies of miliary tuberculosis or because of the progress of the disease in some organ reached by hematogenous distribution, such as, for instance, tuberculoma of the brain.

3. Active intercurrent primary infection. There is healing, with death due to causes other than tuberculosis.

C. Lymphatic blockade:

1. Tuberculous disease with lymphatic blockade. In this group of cases the organ shows gross tuberculosis, but the lymph nodes draining the organ show no fresh tuberculous lesions grossly. Microscopically a few isolated conglomerate tubercles or a few isolated miliary patches of necrosis may be seen.

2. Breakdown of the lymphatic blockade, with production of conglomerate necrotic lesions in the lymph nodes.[10] In this group the lymph nodes of an organ with gross tuberculous disease show conglomerate tubercle or necrosis grossly and microscopically. Microscopic examination is necessary to exclude the possibility of the presence of old lesions which have been hyalinized or have been surrounded by hyaline capsules.

3. Breakdown of the lymphatic blockade with production of massive caseation of the lymph nodes.[10] In this group the lymph nodes draining an organ with gross tuberculous disease show massive caseation grossly. They show one or more large areas of caseation, not merely scattered conglomerate areas of necrosis. In other words, they show the picture seen in a primary infection.

D. Hematic blockade:

1. Tuberculosis with hematogenous blockade. In this group are included all cases of gross tuberculosis of an organ or of an organ system in which no evidence of fresh disease is seen in other organs in the gross, which disease might be interpreted as being due to hematogenous distribution. Microscopically, isolated tubercles or miliary lesions may be observed.

2. Breakdown of the hematogenous blockade with sporadic seeding. In this group other organs, such as the liver, spleen and kidneys, show evidence of soft tubercles or miliary or conglomerate areas of caseation grossly. The organs, however, do not show the regular seeding so characteristic of true miliary tuberculosis. In other words, the lesions appear to be situated haphazardly.

3. Breakdown of the hematogenous blockade with production of true miliary tuberculosis. In this condition there is a diffuse seeding of any or all organs reached by the hematogenous route. The regularity of the seeding and the tendency for the individual lesions to be of about the same size and stage of development are characteristic of miliary

10. There are cases of lymphatic involvement (both C2 and C3) in which lymph nodes throughout the body are attacked.

TABLE 1.—*Classification of Eighty-One Cases of Tuberculosis* *

	Race					Lymphatic Block				Hematic Block			
	White		Negro										
	Number	Percentage	Number	Percentage	Total	White	Negro	Total	Percentage with Block	White	Negro	Total	Percentage with Block
A. Reinfection													
1. Subacute pulmonary tuberculosis	4	9.7	16	47.0	20	2	4	6	30.0	2	7	9	45.0
2. Chronic ulcerative pulmonary tuberculosis	9	22.0	7	20.7	16	5	5	10	62.5	6	7	13	81.3
3. Chronic fibrous pulmonary tuberculosis	18	43.9	4	11.8	22	16	4	20	90.9	14	3	17	77.2
4. Apical pulmonary tuberculosis, with conglomerate lesions	3	7.3	1	2.9	4	3	0	3	75.0	3	0	3	75.0
5. Extrapulmonary tuberculosis	6	14.6	4	11.8	10	4	1	5	50.0	3	1	4	40.0
6. Reactivated primary complex	1	2.5	2	5.8	3	0	1	1	33.3	1	2	3	100.0
Total	41		34		75	30	15	45		29	20	49	
Percentage	54.6		45.4		100	73.1†	44.1†	60.0†		71.6†	58.8†	65.4†	
B. Primary Infection													
1. Active progressive infection	2	66.6	2	40.0	4	0	0	0	0	0	0	0	0
2. Active healing infection	0	0	2	40.0	2	0	0	0	0	0	0	0	0
3. Active intercurrent infection	1	33.4	1	20.0	2	0	0	0	0	1	1	2	25
Total	3		5		8	0	0	0		1	1	2	
Percentage	37.5		62.5			0	0	0		33.3†	20.0†	25.0†	

* A total number of 75 instances of reinfection is listed, as 2 of the 73 patients had both pulmonary and extrapulmonary lesions.
† Percentage of the total in number in each racial group.

TABLE 2.—*Classification of Cases of Tuberculosis with Regard to Breaks of Blockades*

	Total Cases Studied			Lymphatic Break						Hematic Break					
				Conglomerate Areas of Necrosis		Massive Necrosis		Total		Sporadic Seeding		True Miliary Tuberculosis		Total	
	White	Negro	Total	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro	White	Negro
A. Reinfection															
1. Subacute pulmonary tuberculosis	4	16	20	1	5	1	7	2	12	1	3	1	6	2	9
2. Chronic ulcerative pulmonary tuberculosis	9	7	16	2	2	2	0	4	2	1	0	2	0	3	0
3. Chronic fibrous pulmonary tuberculosis	18	4	22	1	0	1	0	2	0	1	0	3	1	4	1
4. Apical pulmonary tuberculosis, with conglomerate lesions	3	1	4	0	1	0	0	0	1	0	0	0	1	0	1
5. Extrapulmonary tuberculosis	6	4	10	0	2	2	1	2	3	0	1	3	2	3	3
6. Reactivated primary complex	1	2	3	0	0	1	1	1	1	0	0	0	0	0	0
Total	41	34	75	4	10	7	9	11	19	3	4	9	10	12	14
Percentage	54.6	45.4	100	9.7*	29.4*	17.0*	26.5*	26.8*	55.8*	7.3*	11.7*	21.9*	29.4*	29.2*	41.1*
B. Primary Infection															
1. Active progressive infection	2	2	4	0	0	2	2	2	2	0	0	2	2	2	2
2. Active healing infection	0	2	2	0	0	0	2	0	2	0	0	0	2	0	2
3. Active intercurrent infection	1	1	2	0	0	1	1	1	1	0	0	0	0	0	0
Total	3	5	8	0	0	3	5	3	5	0	0	2	4	2	4
Percentage	37.5	62.5				100*	100*	100*	100*	0	0	66.6*	80.0*	66.6*	80.0*

* Percentage of the total numbers in each racial group.

tuberculosis in contradistinction to the purely morphologic term "miliary lesions." Individual organs may be spared invasion in certain cases. The characteristic example of this type is miliary tuberculosis subsequent to a primary infection.

Preliminary investigation, as well as a study of the literature, indicates that a purely statistical treatment of the reports of autopsies performed as a routine, not with a special purpose in mind, and executed by many different pathologists give unconvincing results. The small number of cases which a thorough personal study includes is compensated for by the uniformity obtained. Since no absolute lymphatic or hematic blockade is expected, as Ranke himself pointed out, it is important in such a study to apply the same standards uniformly. The critical test, the gross absence of lesions, which separates those cases in which a blockade is present from those in which there is no blockade not only offers a convenient point of division but is of principal importance, since it is universally recognized that primary tuberculosis is, with the rarest exceptions, associated with gross and extensive disease of the adjacent lymph nodes. The number of cases of primary infection in this series is small. The morphologic manifestations of this form of tuberculosis are, however, so well established by abundant reports in the literature that the case reports are presented only as typical examples of a well known entity and in order to contrast the features of primary infection with those of reinfection.

Tables 1 and 2 demonstrate that in all eight cases of primary tuberculous infection there was massive necrosis of the lymph nodes. Likewise, Ghon [11] found that in all but one of one hundred and seventy cases of primary pulmonary infection there was typical involvement of the lymph nodes. That this is true not only in fatal cases of primary infection but indeed in all cases, even those (the great majority) in which no clinical signs or symptoms develop, is proved by the fact that at autopsy the obsolete primary infection is recognized largely by the residual calcification of the nodal portion of the primary complex. Hence, the involvement of the lymph nodes must be considered as an almost invariable component of a primary tuberculous infection, a fact first recognized by Parrot [12] in 1876.

Of the seventy-three cases of reinfection, on the other hand, there was lymphatic blockade in forty-five and massive necrosis typical of the nodes in primary infection in only sixteen. In the fourteen remaining cases gross conglomerate tubercules were present. Yet even these figures do not give an accurate picture of the differences between the two

11. Ghon, A.: The Primary Lung Focus of Tuberculosis in Children, translated by D. B. King, New York, Paul B. Hoeber, Inc., 1916.

12. Parrot, M.: Compt, rend. Soc. de biol. **28**:307, 1876.

groups. Thus, for instance, massive necrosis of any lymph node in the body placed the case in the group of cases of break down of the lymphatic blockade even though all other nodes were essentially free from gross tuberculosis. In eight cases of pulmonary tuberculosis there was a break in the lymphatic blockade only in relation to the abdominal

Fig. 1.—Primary pulmonary tuberculosis. The primary focus was located in the upper lobe of the right lung and produced cavitation. There followed bronchiogenic distribution to the lower lobe of the left lung. Miliary tuberculosis resulted. Note the massive caseous necrosis of the right bronchopulmonary and paratracheal lymph nodes.

lymph nodes, whereas the nodes draining the lungs had perfectly preserved the blockade. Another point which cannot be adequately demonstrated by statistics but which is illustrated by the accompanying photographs (figs. 1 and 2) is the difference between the size of the nodal

lesions in a case of primary infection and their size in a case of reinfection. In the former the most striking lesions of the disease are located in the lymph nodes, whereas in the latter the lesions in the nodes are almost invariably much smaller than the corresponding lesions in the parenchyma. In fact the gross as well as the microscopic examination usually leads to the conclusion that the disease of the nodes in cases of reinfection is of a much more recent date than that of the lungs. It appears that most of the gross lesions develop in the last few weeks of life, during a period when the resistance of the body is broken down. This point is further supported by the fact that in our cases of apical

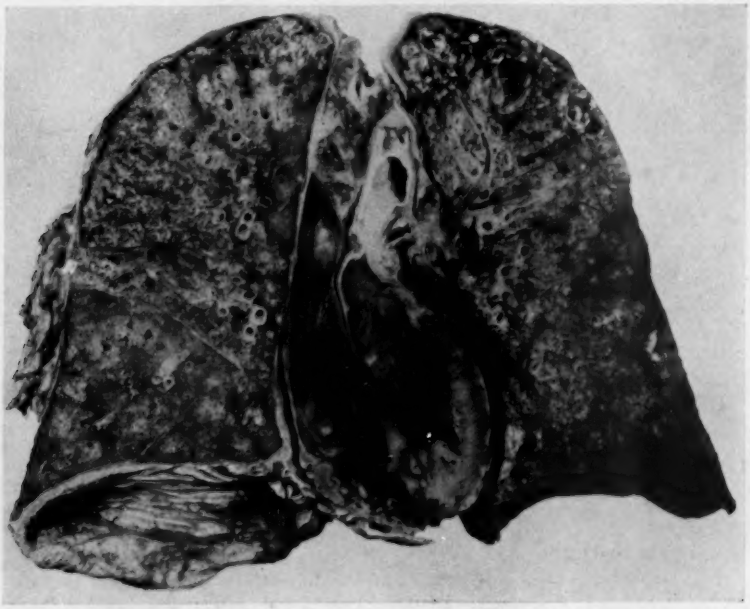

Fig. 2.—The reinfection type of pulmonary tubercuolsis. Note the conglomerate necrosis of the tracheobronchial lymph nodes.

tuberculosis with conglomerate lesions, cases in which the disease was of relatively limited extent and not the cause of death, there was lymphatic blockade. When these criteria are applied, only six of the group of seventy-three cases of reinfection fulfilled these conditions and showed massive caseation which was as extensive in relation to the disease of an organ as that noted in cases of primary infection. The inquiry therefore substantiates Ranke's claims that reinfection is associated with a relatively efficient lymphatic blockade.

In principle, the results of the investigation of the hematic blockade are similar. In forty-nine of the cases of reinfection there was a blockade

of dissemination by way of the blood stream, whereas in only nineteen was true miliary tuberculosis present. In three of these cases dissemination was from an extrapulmonary source, the genito-urinary tract, and in two other cases such an explanation seemed probable. In another case only the liver was affected by the miliary tuberculosis. The seven cases in which sporadic seeding was evident do not fall into the group of cases of miliary tuberculosis. In six of the eight cases of primary infection true miliary tuberculosis was evident. The two cases in which there was no dissemination the patients died not of tuberculosis but of rheumatic pancarditis and of otogenous staphylococcic septicemia, respectively. This is merely an expression of the well known fact that the patient who has a primary tuberculous infection usually dies not because of a pulmonary or intestinal lesion but as a result of hematogenous dissemination from that point. Ghon [11] in his series of one hundred and ninety-eight cases of primary infection obtained evidence of hematogenous dissemination in one hundred and twenty-one. The fact that no hematogenous lesions were observed in our two cases of intercurrent primary infection does not, of course, exclude the possibility that small abortive transmission of bacilli may have taken place. Ranke pointed out that there are all gradations of the amount of dissemination during the secondary stage. In a future publication further substantiation of this statement will be provided.

The Negro patients in our series were a factor definitely tending to decrease the number of cases of lymphatic and hematic blockade. Thus, although 73.1 per cent of the white patients belonged in the group in which a "lymphatic block was present," only 44.1 per cent of the Negroes were represented in this group. In the group of cases in which a hematic block was present the Negroes were represented by only 58.5 per cent, but the white patients were represented by 71.6 per cent. Almost half of the Negroes (47 per cent) had subacute pulmonary tuberculosis, whereas almost half of the white patients (43.9 per cent) had chronic fibrous pulmonary tuberculosis. The type of disease, however, is of distinct importance in the determination of lymphatic and hematic blockade, for the incidence of efficient lymphatic blockade rises from 30 per cent in cases of subacute pulmonary tuberculosis to 90.9 per cent in cases of chronic fibrous tuberculosis, the incidence of efficient hematic blockade being 45 and 77.2 per cent, respectively.

The number of cases of extrapulmonary tuberculosis in this series is too small to permit an examination into Reisner's [13] findings that blockade against an extrapulmonary lesion is less efficient than that against a pulmonary lesion. It is perhaps suggestive that in 50 per cent

13. Reisner, D.: Am. Rev. Tuberc. **30**:375, 1934.

of the cases of extrapulmonary lesions there was a break in the lymphatic blockade and in 75 per cent a break in the hematic blockade. That chronic tuberculous disease of the lungs is rarely associated with the same condition in any other organ, however, is shown by the fact that in only two of our cases was there associated pulmonary and extrapulmonary disease. Involvement of organs communicating with the affected organ, such as the larynx and the gastro-intestinal tract with the lung, is, of course, merely infection by continuity and therefore does not controvert this rule.

These results must be interpreted as a manifestation of resistance. The condition of the lung in cases of chronic pulmonary tuberculosis apparently contradicts this, since the organ is often completely destroyed. The dilemma is resolved, however, if immunity in tuberculosis is considered to be of a lesser degree and probably of an entirely different character from that of such diseases as measles and smallpox. The degree of resistance here is not sufficient to prevent the development of clinically apparent disease in organs whose preexistent channels of communication, such as the bronchi of the lungs and the tubes of the genito-urinary tract, are avenues by which the disease is easily diffused. In such instances destructive disease occurs; the forces of resistance, however, are sufficient to prevent the spread beyond the organ attached. The blockade cannot be purely mechanical, such as would be produced by obliteration of the lymphatic system and fibrosis of the nodes. Lymph, inflammatory exudate and tubercle bacilli reach the nodes, which are frequently large and succulent. On microscopic examination the lymphatic sinuses are observed to be filled with proliferated and desquamated endothelium, and not infrequently tubercles are seen. Tubercle bacilli, moreover, have been demonstrated in the blood stream of persons suffering from active pulmonary tuberculosis. It must therefore be assumed that the bacilli pass in relatively large numbers from the lesions in the lung into the nodes and the blood stream, where, however, they are destroyed or succeed at the most in producing small proliferative and nonprogressive lesions. Naturally, as a terminal event, a break in the blockade may occur. Immunity in tuberculosis is therefore largely the result of a localization of the disease, certainly as much a sign of resistance as in the pyogenic infections, in which the development of an abscess demonstrates the ability of the body to localize the infection and the development of septicemia demonstrates an inability to do so. It must not be assumed that such localization necessarily leads to a cure; on the contrary, as in meningococcic infections, the very localization may lead to a fatal though localized disease.

In order to appreciate the value of this trend to localization in cases of reinfection, it is necessary to consider the status in cases of primary infection. In the eight cases of primary infection in this series the

classic morphologic picture was exhibited. Gross caseation of the lymph nodes has been present in almost every described case of primary infection, and usually the mass of the lesions in the nodes is four or five times as large as that in the lungs. Animal experimentation as well as the study of the postprimary tubercles in man indicates that the bacilli pass very early from the nodes into the blood stream and frequently succeed in producing lesions. Massive hematogenous distribution, that is, miliary tuberculosis, is particularly characteristic of primary infection. In patients less than 5 years old, in whom it is usual to observe only primary infection, 59 per cent of the deaths from tuberculosis were due to the meningeal and disseminated forms,[14] i. e., miliary tuberculosis, whereas of the deaths of patients of all ages, only 5 per cent fell into this group.[15] This difference is caused not solely by age, since in adults miliary tuberculosis in its generalized or localized forms is the usual cause of death in cases of fatal primary infection. There seems, therefore, to be no reasonable doubt that in cases of primary infection diffusion of the disease tends to occur and is much more pronounced in patients less than 5 years old. In cases of reinfection, on the other hand, the disease is usually localized, no matter how severe the local manifestations may be.

Animal experimentation has led most workers in this field to acknowledge the existence of acquired resistance. It is difficult to interpret the Koch-Roemer experiment in any other fashion. Pinner's [16] translation of Koch's original report read as follows:

> If a healthy guinea pig is injected with a pure culture of tubercle bacilli, the puncture wound usually closes and appears to heal within a few days; only gradually in the course of the next ten to fourteen days a firm nodule develops which soon ulcerates and remains as an ulcerated area until the animal dies.
>
> However, an entirely different condition prevails if a guinea pig is injected which is already tuberculous. The best animals for this purpose are those which were successfully inoculated six weeks previously. In such animals the small wound also closes in the beginning but no nodule develops; already on the third day a peculiar change occurs at the area of injection. It indurates and takes on a dusky hue which is not only found at the point of injection itself but spreads out over the neighboring territory for a distance up to 1 cm.
>
> Within the next few days it becomes increasingly apparent that the altered skin is necrotic; finally it sequesters and a shallow ulceration remains which usually heals quickly and permanently without infecting the neighboring lymph nodes.

To the interpretation of this phenomenon as a manifestation of resistance the objection has been raised that necrosis, which in internal

14. This is the nomenclature of the statistical study quoted. We do not assume that tuberculous meningitis is necessarily the result of direct infection of the meninges by way of the blood stream.[8]

15. Whitney, J. S.: Facts and Figures About Tuberculosis, New York, National Tuberculosis Association, 1931.

16. Koch, Robert: Am. Rev. Tuberc. **25**:285, 1932.

organs leads to the formation of cavities, is one of the most serious complications of tuberculosis. Caseation and liquefaction are, however, not a necessary result of the immunologic forces active in reinfection. Baldwin and Gardner [8] infected guinea-pigs with the almost avirulent R1 strain of tubercle bacilli and then reinfected them by the inhalation method with a highly virulent human strain. The disease produced in these animals was slower in progression and less extensive than in the controls which had not received the first infection with the R1 strain. Caseation was rarely observed; the lymphatic tissue both in the lung and in the tracheobronchial nodes showed no specific changes, no caseation and little or no fibrosis (lymphatic block). Paterson [17] injected virulent human tubercle bacilli into the pleural cavities of guinea-pigs. In animals which had been previously infected or vaccinated with tubercle bacilli, an acute illness and acute serofibropurulent pleurisy developed. With the exception of four immediate deaths, the animals that survived this stage lived for seventy or more days and showed chronic fibrous tuberculosis (hematic block), whereas the previously uninfected controls did not show acute manifestations but died of acute disseminated tuberculosis on an average of from twenty-eight to thirty-five days after the first injection. Krause [18] has demonstrated that the bacilli of reinfection suffer a retardation in their spread from the point of injection. Soper and Dworski [19] vaccinated rabbits with living tubercle bacilli and protected them thereby against intracisternal injections of virulent bovine organisms. Most of the animals showed clinical evidence of mild meningeal inflammation, which at autopsy was evidently healing. The untreated controls died of tuberculous meningitis. Soper [20] reinfected the livers of rabbits by way of the mesenteric veins with bovine organisms. Tubercles developed; but these were absorbed, and no evidence of disease was seen later in other members of the series. In the control animals, not previously infected, more tubercles developed and they were not absorbed as fast as were the tubercles in the infected animals. The intratracheal introduction of tubercle bacilli into infected animals [21] produces an acute pneumonic infiltration which, like the resolving exudates seen in tuberculosis in man,[22] may be completely resorbed without undergoing liquefaction. Thus, there is every reason to regard the Koch-Roemer subcutaneous experiment as furnishing a special instance of a general law active in acquired resistance to tuber-

17. Paterson, Robert C.: Am. Rev. Tuberc. **1**:353, 1917.
18. Krause, A. K.: Am. Rev. Tuberc. **14**:211, 1926.
19. Soper, W. B., and Dworski, M.: Am. Rev. Tuberc. **21**:209, 1930.
20. Soper, W. B.: Am. Rev. Tuberc. **1**:385, 1917.
21. Austrian, C. R., and Willis, H. S.: Am. Rev. Tuberc. **14**:306, 1926. Soper, W. B.; Sampson, H. L., and Haskins, C. H.: ibid. **15**:88, 1927.
22. Reichle, H. S.: Am. J. Dis. Child. **45**:307, 1933; **46**:969. 1933.

culosis. Moreover, there is no necessity of assuming that a permanent lesion or liquefaction of tissue must result from this mechanism. Indeed, it is probable that the clinical cases of reinfection tuberculosis represent only those cases in which resistance has failed. The clinician cannot recognize the many cases in which reinfection, like the majority of primary infections, develops and comes to a quiescent stage without the manifestation of any clinical signs or symptoms. The pathologist observes evidence of "healed" reinfection almost as often as he does the results of primary infection. Thus Aschoff [23] said:

> Careful observation at all autopsies in the past two years has shown that the number of reinfection scars is not less than the number of primary infection scars; that is, over 90 per cent of all adults possess not only a primary but also a reinfection scar. It therefore follows that phthisical reinfection is as completely conquered by the majority of human beings as primary infection.

Opie [24] found that the percentage of cases of "encapsulated apical tuberculosis" increased with the age of the subjects and reached a maximum of 50 per cent in the group of subjects over 70 years of age. Of the subjects at this age, 16.7 per cent showed scars within the apex, probably tuberculous, and 33 per cent showed an induration of the apical pleura, possibly tuberculous. Opie said: "With one exception the apical lesion (in 8 instances) has pursued a chronic course and, encapsulated by fibrous tissue, has remained limited to the extreme apex of the lung."

It is frequently, but erroneously, assumed that pneumonic infiltration and especially caseation are caused solely by the changed reaction of the body consequent to the primary infection. However, the primary focus, the earliest lesion in the body and one which is forming at a time when sensitivity to tuberculin (allergy) has not yet developed, is the result of pneumonia. Study of primary infection in man and in animals,[25] the presence of elastic fibers in the center of old primary foci and the microscopic structure of the earliest primary focus yet discovered in man [26] have established this fact. Furthermore, it has been shown by Zarfl [26] that the pneumonic lesions contain innumerable tubercle bacilli. The bacteria multiply apparently without hindrance in this early stage of the disease. In cases of reinfection, on the other hand, the demonstration of tubercle bacilli in a tissue which is the seat of undoubted tuberculosis is usually a tedious process. In a study of tissues removed at the Cleveland City Hospital because of tuberculosis and which pre-

23. Aschoff, L.: Klin. Wchnschr. **8**:1, 1929.

24. Opie, Eugene L.: J. Exper. Med. **26**:263, 1917.

25. Huebschmann, P.: Pathologische Anatomie der Tuberkulose, Berlin, Julius Springer, 1928, p. 164.

26. Zarfl, M.: Ztschr. f. Kinderh. **5**:303, 1913.

sented the classic morphologic features of tuberculous granulomatous inflammation, tubercle bacilli were observed in only 25 per cent of the cases. When demonstrated the micro-organisms were present only in small numbers, except in lesions where widespread caseation and the absence of a tissue response indicated that the subject had lost his power of resistance. It appears that the immune forces are capable of affecting tubercle bacilli so that they lose their distinctive tinctorial properties and probably also their virulence. Manwaring and Bronfenbrenner [27] have demonstrated a reduction in the number of tubercle bacilli in the peritoneal exudates of reinfected guinea-pigs. Lurie [28] has shown that virulent bovine bacilli will not grow unrestrictedly in the livers of previously infected rabbits. The immediate multiplication seen in the livers of animals primarily infected by way of the mesenteric veins is missing, and Lurie expressed the belief that the reinfecting organisms are largely destroyed in the immune animals. This ability to inhibit the growth of tubercle bacilli must be one of the important factors in the resistance shown by reinfected animals and man and deserves more intensive study.[8] In its early stages the primary infection shows an unimpeded growth of the infecting bacilli. Woodruff [29] has demonstrated this period of free growth by a study of the omentum of the guinea-pig. It was observed only in previously uninfected animals (primary infection), not in reinfected animals. The freely growing bacilli disappeared rapidly after the seventh day (the period of development of the tubercle and of sensitivity to tuberculin). The work of Gaiginsky and Laporte [30] must be interpreted in like manner.

These observations have convinced most observers that acquired resistance to tuberculous infection exists. Furthermore, it is probable that this resistance continues, although perhaps to a lesser degree, after the lesions become clinically quiescent and possibly ceases when the primary complex and its subsidiary lesions heal completely. On the other hand, for man there are as yet no data which permit even a provisional statement concerning the relative importance of acquired as contrasted with native resistance.

27. Manwaring, W. H., and Bronfenbrenner, J.: J. Exper. Med. **18**:601, 1913.
28. Lurie, M. B.: J. Exper, Med. **50**:747, 1929.
29. Woodruff, C. E.: Am. J. Path. **10**:739, 1934.
30. Gaiginsky, A., and Laporte, R.: Compt. rend. Soc. de biol. **117**:569, 1934.

PATHOGENESIS AND HISTOPATHOLOGY OF EXPERIMENTAL PNEUMONIA IN RATS

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CHICAGO

No attempt to review the literature on experimental pneumonia will be made at this time as adequate reviews have been published by several authors. Among the best are Wadsworth's,[1] published in 1904, and Lindau's,[2] published in 1933.

Little difficulty has been encountered in producing pneumonia of the circumscribed or "patchy" type (bronchopneumonia) by intratracheal injection of virulent bacteria, but few attempts have been uniformly successful in producing a diffuse lobar type (croupous) of pneumonia in laboratory animals. The chief difficulty seems to have been encountered in finding a suitable susceptible animal and in adapting the virulence of the organism to that animal. In animals which are highly susceptible to pneumococcic infections, such as the mouse and the rabbit, fatal septicemia frequently supervenes after the injection of virulent bacteria before the exudative process in the lungs is fully developed. Wadsworth [1] was successful in circumventing this result by partially immunizing rabbits to the pneumococcus before giving the intratracheal injections of the infecting dose. In this way it was possible to induce diffuse exudative pneumonia in a few rabbits without causing overwhelming bacteremia.

The report of the first consistent results was published in 1920 by Blake and Cecil.[3] Their experiments were performed on monkeys. Small quantities of bouillon cultures of pneumococci were injected intratracheally, and the lobar pneumonia which resulted resembled in its course and microscopic pathologic picture the spontaneous disease in man.

The dog has been found to be relatively resistant to the disease, and most authors have found it necessary to inject massive doses of pneu-

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1. Wadsworth, A.: Am. J. M. Sc. **127**:851, 1904.
2. Lindau, A.: Acta path. et microbiol. Scandinav. **10**:1, 1933.
3. Blake, F. G., and Cecil, R. L.: J. Exper. Med. **31**:403, 1920.

mococci in order to produce anything more than an abortive infection in this animal. In the earlier work such inoculations often resulted in generalization of the infection and a fatal termination. The most successful experiments on the dog have been performed by Robertson and his co-workers,[4] who obtained consistent results by injecting small doses of virulent pneumococci far down into the bronchi through a radio-opaque catheter under the fluoroscope. The bacteria were suspended in a starch broth paste, which effectively protected them from the defenses of the tissue during the first few hours of developing pneumonia. In their opinion the edema fluid which appears in the development of the inflammatory lesion supplies for the pneumococci the necessary protection from phagocytosis as well as furnishes an excellent medium for their rapid growth.[4c]

In 1932 Nungester, Wolf and Jourdonais [5] observed that the effective virulence of bacteria when injected into the peritoneum of mice could be greatly enhanced by suspending the cultures in sterilized gastric mucin. The same mixture was used by Nungester and Jourdonais [6] for intrabronchial injections in attempts to produce pneumonia in rats. They [7] devised a method for inoculating small animals intrabronchially by means of a cannula and a fine catheter, and they were consistently successful in inducing pneumonia in rats by the injection of virulent pneumococci, in doses as small as 0.000005 cc. of a twenty-four hour bouillon culture (representing roughly about 1,000 cocci per dose, estimated by plating).[6]

EXPERIMENTAL OBSERVATIONS

For the present studies one hundred and ten rats, including control animals, were given injections by this method and were killed at intervals ranging from one hour to eleven days. For most of the experiments a broth culture of type III pneumococci (obtained from Dr. L. Webster) was used in doses of 10^{-4} cc. in 0.1 cc. of sterile mucin (relative viscosity, 4.5 to 5). In some cases smaller doses were used (10^{-5} and 10^{-6} cc.). The larger dose was frequently fatal within two or three days. In a small series diluted india ink was added to the mucin and bacteria in order to aid in locating exactly the area of injection. In the first stages of the inflammatory process the mucin could be identified easily in stained sections, but later it was either obscured by the exudate or absorbed. The animals were killed with ether, and the lungs were hardened in toto in Bouin's fluid or in Helly's fluid (Zenker's solution to which a dilute solution of formaldehyde has been added). Collapse of the lungs was prevented by clamping the trachea

4. Terrell, E. E.; Robertson, O. H., and Coggeshall, L. T.: J. Clin. Investigation (*a*) **12**:393, 1933; (*b*) **12**:433, 1933; (*c*) **12**:467, 1933.

5. Nungester, W. J.; Wolf, A. A., and Jourdonais, L. F.: Proc. Soc. Exper. Biol. & Med. **30**:120, 1932.

6. Nungester, W. J., and Jourdonais, L. F.: J. Bact. **29**:34, 1935.

7. Jourdonais, L. F., and Nungester, W. J.: Science **81**:74, 1935.

before opening the chest cavity. The stains used were hematoxylin and eosin, Mallory's phosphotungstic acid-hematoxylin stain for fibrin and the Gram-Weigert method for bacteria.

In the stages of development of the lesions up to twelve hours, wide variations in the extent of the lesions were noted even in animals that had been given the same doses at the same time. This was due in part to differences in the distribution of the inoculum in the lungs. When the entire dose reached the periphery of the left lung or the lower lobe of the right lung, as was observed to be the case in most of the animals, much less variation was noted, and after twelve hours the extent and stage of development of the lesions were remarkably consistent. When variations in the extent and quality of the exudate of lesions occurred in animals that had been given injections at different times, it is possible that variation in the virulence of the strains of pneumococci was a more important factor. Furthermore, differences in the susceptibility of the animals cannot be ignored, particularly since the rats were obtained from different sources. For this reason the histologic picture observed in the majority of the animals for a given period will be regarded as typical for that period, and in the description of the lesions the variations from this "typical" picture will be noted.

In the normal lung of the rat the epithelial cells which help to form the alveolar walls are flat and inconspicuous. Their nuclei are oval or disk-shaped, staining rather darkly with hematoxylin and having one or more small granules of chromatin. Most of the capillaries are so small as to be almost indistinguishable except by the large pale nuclei of the endothelial cells in the alveolar walls (fig. 1 *A*). In almost every lung examined slight irritative lesions or small foci of chronic inflammation could be observed in some part. In most cases small accumulations of lymphocytes were present in the tissue around large bronchi, and in many cases large lymphoid mantles surrounded the secondary and tertiary bronchi. These were rarely involved in the pneumonic process in the early stages, since they are centrally located, but in later stages they showed evidence of inflammation in the form of histiocytic hyperplasia and occasionally in the appearance of large follicles. In small scattered areas, usually at the periphery of the lung, the air sacs contained a few alveolar phagocytes filled with fine colorless or light brown granules. In interpreting the histologic picture in these animals, therefore, it is necessary to take into account the possibility of the presence of complicating spontaneous lesions that are chronic and inflammatory.

Within a few hours after the injection the mucin was recognizable as a granular and amorphous basophilic substance widely distributed in the small bronchi and alveoli. It was stained consistently but faintly with hematoxylin and strongly with methyl violet in the sections treated with the Gram-Weigert stain (fig. 1 *B*). The lining of a few of the

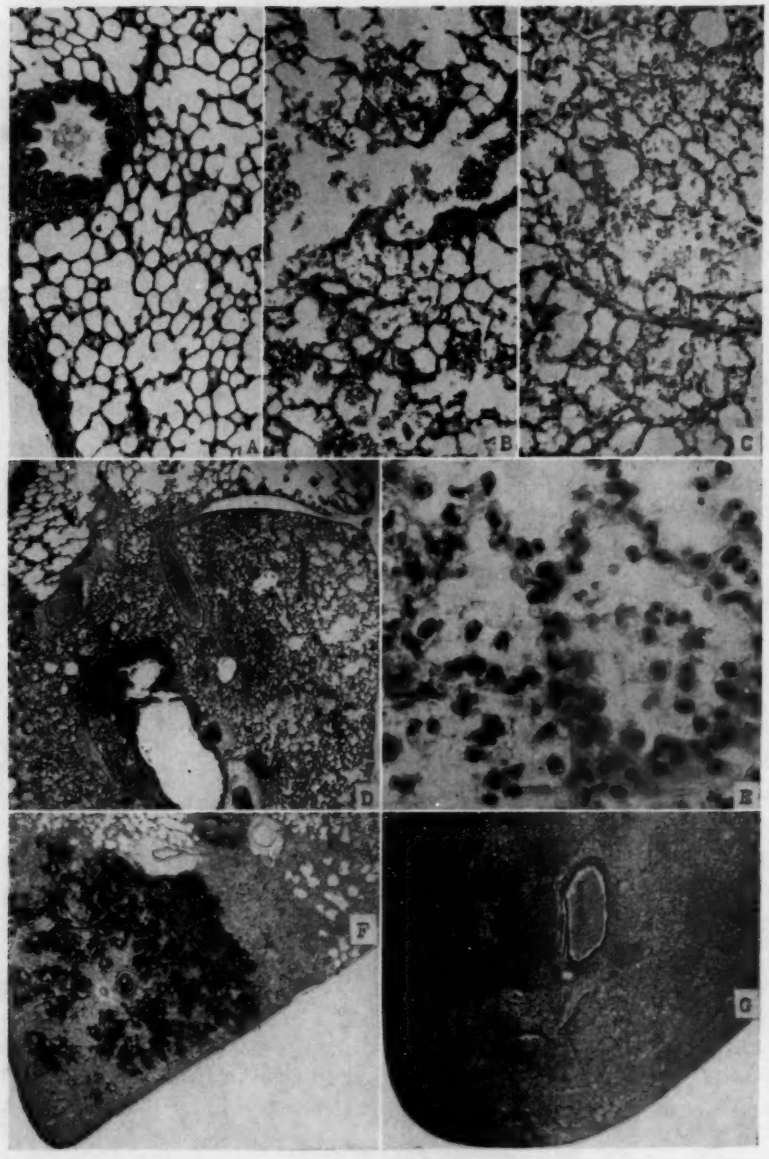

Figure 1

EXPLANATION OF FIGURE 1

Fig. 1.—*A*, normal lung (hematoxylin and eosin stain). Two large bronchi partly surrounded by thin mantles of lymphocytes are seen at the left. *B*, one hour after intrabronchial insufflation of mucin alone (Gram-Weigert stain). The mucin is evenly distributed through the alveolar spaces and partly fills the lumen of a terminal bronchiole (upper right). Little alteration of the alveolar walls has occurred. *C*, four hours after insufflation of pneumococci (10^{-5} cc. of bouillon culture in 0.1 cc. of mucin); hematoxylin and eosin stain; same magnification as in *A* and *B*. The mucin is stained faintly with hematoxylin. Proliferation and swelling of septal cells have produced uneven thickening of the alveolar walls. Few leukocytes are present in this area. *D*, a section from the middle of the lower lobe of the right lung five hours after inoculation with pneumococci (10^{-4} cc. in 0.1 cc. of mucin); hematoxylin and eosin stain. In this case the mixture was injected into the middle part of the lobe. The exudate spreads in all directions with interruption at an interlobar fissure (upper right). The lumens of the large bronchi are clear at this stage. *E*, high power photomicrograph of the section shown in *D* (hematoxylin and eosin stain). Swollen septal cells are beginning to appear in the alveolar spaces, and polymorphonuclears are fairly numerous. The cloudiness in the alveoli is due to the presence of faintly stained mucin and edema fluid. *F*, the base of the left lung, six hours after inoculation (hematoxylin and eosin stain). The lower right margin is the diaphragmatic surface, and the left margin is posterior. In this case the ink was distributed in a comparatively small area. Edema fluid and cellular exudate have obliterated the air spaces in the whole area of inoculation and have spread well beyond it in an irregular zone, leaving many vacuoles in the edema zone. *G*, the area of consolidation in the middle lobe of the right lung at nineteen hours (hematoxylin and eosin stain). The exudate is largely cellular and involves about nine tenths of the lobe.

larger bronchi was thinly coated with mucin, but rarely was the lumen of any bronchus completely filled with the material. This was not true of the lungs into which india ink was injected. In those cases the injection mass was not so widely disseminated, small groups of alveoli were almost solidly filled with carbon-mucin mixture and a few of the smaller bronchi and bronchioles were completely filled with the mass (fig. 1 *F*). In later experiments we observed that by further diluting the ink (1:40) the concentration of the mixture in limited areas could be avoided. The evolution of the lesion was not appreciably affected by the presence of the ink in either the more concentrated or the dilute mixtures.

LESIONS IN EXPERIMENTALLY INFECTED ANIMALS

After One Hour (Seven Rats).—At the end of one hour, slight but definite alteration of the tissue was apparent. The alveolar epithelium was unevenly swollen. Occasional epithelial cells projected prominently into the lumen, and a few rounded cells were free in the air spaces. A few polymorphonuclear neutrophils were seen in the alveolar septums. Frequently it was impossible to determine whether they were within the capillaries or the intercellular spaces. The capillaries were slightly dilated, and within many of them a single column of blood cells could be seen, whereas in normal areas the alveolar walls were, for the greater part, collapsed. Bacteria were so few that only rarely were they noted in the sections. The swelling of the alveolar cells was general throughout the mucin-bearing tissue but was strictly confined to it. No alteration whatever was seen in the rest of the lung, unless it was slight hyperemia in an indefinite zone just beyond the area containing the injection mass.

Sections from the lungs of animals that had received mucin alone showed about the same type and degree of alteration at this period (one hour) as did those of animals which received pneumococci in mucin.

In the lungs containing carbon the alteration was even less conspicuous than in the former cases, probably owing to the fact that the injection mass was not so widely distributed and was not in such close contact with the alveolar walls as in those which did not receive carbon.

After Two Hours (Five Rats).—In this period sections from the area into which the material was injected (which was recognizable grossly in only two cases as a faintly hyperemic patch on the pleura) revealed a general thickening of the alveolar walls in the involved tissue, i. e., in the area in which mucin was seen. The thickening was due to swelling of the septal cells and dilatation of the capillaries. Many of the swollen epithelial cells projected prominently into the alveolar spaces. Very few were detached from the walls. Occasional pigment-laden macrophages were seen within the interstices of the septums and free in the alveoli, but these were seen also in lungs into which no material had been injected. Evidence of hyperplasia of the septal cells was present in the form of occasional mitotic figures.

After Three or Four Hours (Seven Rats).—The characteristic alterations for these two periods are described together, since the single animal representative of the three hour period showed about the same degree of advancement of the lesion as some of those representing the four hour period.

In all the animals of this time interval the lesion was recognizable on the pleural surface of the lung as a deep pink or pinkish-gray slightly translucent area at the base of the left lung or of the lower lobe of the right lung. The area

was not elevated and usually extended from the lower part of the posterior surface to the base (diaphragmatic surface), involving only a small portion of the latter. The size of the surface area varied from 2 by 3 mm. to 10 by 6 mm. in diameter and was dependent entirely, as proved by microscopic sections, on the distribution of the injected mixture.

All the elements of alteration that were observed at the end of the two hour period were present also at three and four hours but in a more marked degree (fig. 1 *C*). The hyperemia was considerably greater. Swelling and proliferation of septal cells were prominent. Polymorphonuclears were much more numerous. In some areas they were present in large numbers in the air spaces, mixed with the mucinous injection mass, a few erythrocytes and scanty edema fluid (eosinophilic albuminous coagulum). Abundant erythrocytes were seen in a few animals. A small number of mononuclear cells with nuclei identical with those of the attached septal cells were free in the air sacs, mixed with neutrophils and rare eosinophils. In exceptional cases bacteria were fairly numerous in a few areas, as many as a dozen or more pairs being noted in each of several alveoli. Most of the bronchioles in the area of inoculation contained eosinophilic albuminous substance (edema fluid). Several of the bronchi in which mucin could be seen contained leukocytes mixed with the injection mass, which in the larger bronchi was located at the periphery of the lumen. The bronchial epithelium was swollen, and an increased number of mitotic figures were observed in the cells of some of these, especially of the smallest bronchi and bronchioles in contact with the infectious mixture.

After three or four hours fibrin first appeared as clumps and threads of fine black granules in sections stained with phosphotungstic acid hematoxylin. The area of distribution of the fibrin was practically coextensive with the area of distribution of the injection mass (colorless or faintly yellowish amorphous masses), but the relative abundance of fibrin bore no relation to the number of leukocytes in the alveoli.

After from Five to Eight Hours (Twelve Rats).—The gross appearance of the lungs at this period was the same as that at four hours, with the exception that the area visible on the pleural surface over the site of injection was light reddish brown. The reason for the change in color was explained by the altered microscopic appearance.

With the exception of a few open spaces, the tissue in the area of injection was filled solidly with edema fluid and cells, the latter consisting largely of polymorphonuclears (figs. 1 *D* and *E*). Detached septal cells were present in small numbers in all areas among the cells in the exudate, and in a few alveoli they constituted the majority of cells. Many of them contained granules of phagocytosed material. In the lungs in which india ink formed part of the injected mixture the margin of exudate consisting of edema fluid could be seen to have advanced well beyond the area of injection in the direction of the hilus (fig. 1 *F*). In the advancing zone leukocytes were generally less numerous than in the older part of the lesion. The presence of carbon-filled macrophages and polymorphonuclears in the outer margin of the edema zone and beyond suggested a possible means of spread of the bacteria from infected to uninfected tissue. Eosinophils did not constitute a prominent part of the leukocytes except in the perivascular and peribronchial areolar tissue, where they frequently predominated. The capillaries were unevenly distended in the area of injection. In some places the erythrocytes outnumbered the leukocytes in the exudate. They were a prominent element only in the region of the injection at this stage.

Bacteria were still not numerous in the majority of cases. Only occasional pairs or single cocci were seen in the cytoplasm of neutrophils. In a few places small clumps of extracellular bacteria were encountered in the alveolar spaces.

After from Ten to Twelve Hours (Eight Rats).—In the specimens representing this group the lesions varied in extent from 4 mm. in diameter to nine tenths of the postcardial lobe (about 10 by 8 by 5 mm.).

The feature that distinguished this from previous stages was the relative density of the exudate. Leukocytes, fibrin and erythrocytes were more abundant, and in the older part of the lesion the cells were packed together solidly, completely filling the alveoli. Bacteria were generally more numerous than they had been at previous stages.

After Nineteen Hours (Six Rats).—At this stage definite zones could be recognized macroscopically by inspection of sectional surfaces of the consolidated lung. The older part of the lesion, practically always located at the base, was gray or gray-brown (black when ink had been injected). Above it there was a comparatively wide zone of red exudate. Usually a narrow pinkish-gray zone was visible next to the red zone and formed the advancing margin of the lesion. Both the gray and the red zone were firm, homogeneous and airless. In one rat the pneumococcus-mucin-ink mixture was distributed in the parenchyma of the middle third of the left lung. In this case the exudate spread toward the apex and toward the base for approximately equal distances from the ink-bearing area.

Histologically, this stage was characterized by solid leukocytic exudate (fig. 1 *G*), a wide zone of edema and extremely numerous bacteria. Pneumococci were most numerous just beneath the pleura and least numerous in the zone of edema at the advancing zone of exudate. However, a few were noted far out in the edema zone and in the edema fluid within the bronchi. In the older part of the lesion fine nets of fibrin were irregularly distributed through the solid leukocytic exudate. In the more recent part of the lesion, just behind the advancing edema zone, much of the stainable fibrin was in the form of coarse and fine granules and thick short strands mixed with the leukocytes. erythrocytes and bacteria. As a rule the lesions showing the most abundant fibrin contained large numbers of erythrocytes and pneumococci and, conversely, lesions containing very few cocci were poor in fibrin.

After Twenty-Four Hours (Seventeen Rats).—At the end of a twenty-four hour period further extension of the pneumonia had occurred to involve as much as the lower half of the left lung (three animals), or practically complete consolidation of the lower lobe of the right lung (four animals). In a few of the rats showing less extensive involvement the first evidence of beginning resolution was observed in the oldest part of the lesion, namely, small irregular areas containing mononuclear phagocytes and few or no polymorphonuclear leukocytes in the otherwise solid leukocytic fibrinous exudate. These were located either around large bronchi or just beneath the pleura. In the more extensive lesions the edema zone was relatively wide, while in the lesions limited to a smaller mass of tissue the edema zone was narrow or not distinguishable. The advancing margin of the edema zone was irregular; even in its broadest portion the tissue was not solidly filled with edema fluid (eosinophilic protein precipitate) but contained numerous round air spaces (single distended alveoli) and groups of overdistended alveoli (figs. 1 *F* and 2 *A*). Sections stained for bacteria and fibrin showed in many of the alveoli in the edema zone compact masses of pneumococci enmeshed in coarse fibrin nets (fig. 2 *A*). Fibrin was extremely abundant in the lesions of several members of this group. In four animals that died at twenty-four hours complete

lobar consolidation had occurred; microscopically the exudate was uniform throughout the lobe, consisting largely of leukocytes and fibrin, the latter forming a dense network in the parenchyma, and in some instances fibrinocellular plugs were present in the small and large bronchi (figs. 2*C* and *D*).

After from Thirty to Forty-Eight Hours (Twenty-One Rats).—During this period the alteration was one of extent of the lesion rather than of quality of the exudate or degree of alteration of the parenchyma. Fibrin was most abundant in animals that died or those that were killed within from twenty-four to forty-eight hours. In the animals that died, bacteria were extremely numerous throughout the involved tissue. In those that survived in good condition and were killed at this time, bacteria were fewer than in earlier stages. At forty-eight hours evidence of beginning resolution was present in practically all the pneumonic lungs examined. In those containing the india ink "tracer" these poorly defined areas of resolution were seen within and around the margins of the larger ink deposits. Leukocytes and bacteria were absent from these, and macrophages were the only free cells in the alveoli. Many of the phagocytes contained carbon. Outside the area of injection fibrin did not appear to be reduced at this period, and its meshes were filled with finely granular protein fluid (fig. 2*B*).

After from Three to Eleven Days (Twenty-One Rats).—Shrinkage of the exudate from the alveolar walls began to appear at the end of three days. This did not occur uniformly throughout the lung but seemed to depend on the presence of abundant fibrin. In alveoli in which stainable fibrin was scanty or absent, no separation between the alveolar wall and the exudate appeared. After contraction of the fibrin the intact alveolar septum stood out sharply in contrast to the obscure outlines of the alveoli which were closely filled with exudate. At this stage the septums were thin, and the capillaries were inconspicuous, as they contained little or no blood (fig. 2*E*).

In some cases resolution was well established at three days. In the lung of one of these rats resolution was almost complete in the center of the area of distribution of the carbon. Many alveoli contained only a few macrophages and scanty granular débris, and fibrin was strikingly less abundant than in the tissue just outside the ink-bearing area (fig. 2*C*). It is noteworthy that all the bronchi in this clearing area were completely filled with plugs of fibrin enmeshing a few leukocytes, but macrophages were absent from the bronchial lumens (fig. 2*D*). All the rest of the lung (left) was solidly filled with fibrinocellular exudate except for a wide zone of edema in the upper part, including the apex. This zone contained large numbers of pneumococci, few leukocytes and no fibrin. Carbon-laden macrophages were disseminated throughout the lung, including the edema zone around the apex.

Such wide differences in degree of resolution were noted in the animals that survived and were killed with ether at different intervals between three and eleven days that no stage can be described as "typical." Some showed resolution and reaeration of the oldest part of the lesion, i. e., that part which received the carbon-bacteria mixture, at the end of three days, while others showed only small patches of beginning resolution at the end of nine days. The shortest period in which resolution was completed in an entire lobe was nine days. Evidence of pneumonia was still clearly recognizable in some lungs at the end of eleven days in the form of thickened bronchial epithelium after regeneration and small foci of lymphoid cells scattered through the parenchyma (fig. 2*F*). How much accumulation of lymphoid tissue around the bronchi had occurred during the pneu-

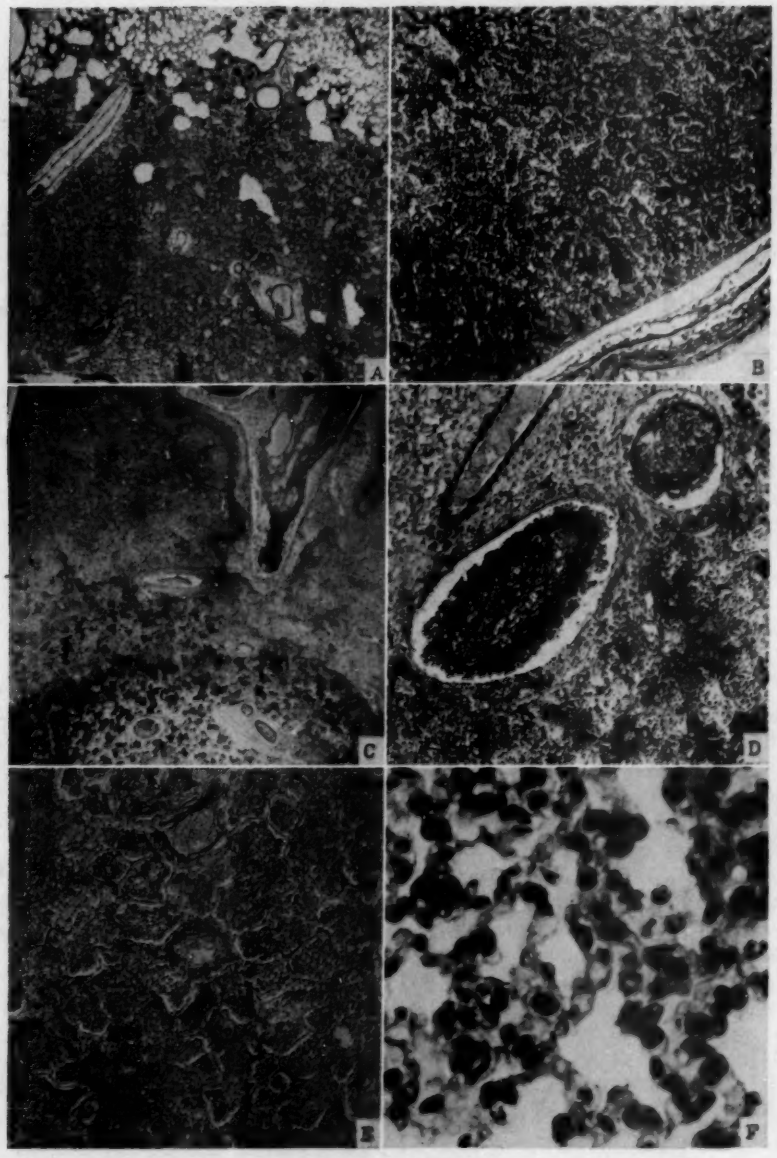

Figure 2

EXPLANATION OF FIGURE 2

Fig. 2.—*A*, section of the left lung twenty-four hours after inoculation, showing zones of exudate (Gram-Weigert stain). Edema fluid has extended into the normal tissue along an irregular margin (upper third of the figure), leaving vacuoles in the otherwise solid exudate. The small black spots in the edema zone represent small "colonies" of pneumococci enmeshed in fibrin. The solid gray area consists of leukocytic exudate with relatively scanty fibrin; the darker patches at the lower border are denser masses of fibrinous exudate. *B*, after two days (Gram-Weigert stain). A network of fibrin is seen within the alveoli and fibrinous exudate on the pleural surface (lower right). The gray "fuzzy" areas in the lower left corner of the figure are areas of hemorrhagic exudate. *C*, after three days (Gram-Weigert stain). Both large and small bronchi are filled with fibrin plugs. The india ink "tracer" appears as small black patches in the lower half of the figure, and between the patches are light areas representing the site of beginning resolution. From this site the fibrin has disappeared, except that in the bronchi. *D*, higher magnification of the area of beginning resolution shown in *C*. The coarse black masses are carbon. Most of the fibrin has disappeared. The lumens of both bronchi in the field are filled with dense nets of fibrin, and the degenerated desquamated bronchial epithelium is adherent to the exudate. Carbon-filled macrophages are numerous in the alveoli but have not reached the bronchial lumens. *E*, after five days (phosphotungstic acid hematoxylin stain). The mosaic appearance is due to shrinkage of the exudate (probably an artefact) in an area containing abundant fibrin. The alveolar walls are intact and thin, as in a normal lung. *F*, after eleven days resolution has occurred. The exudate has been completely removed from the alveoli, but the septums remain thick, owing to persistent swelling and hyperplasia of the septal cells. The capillaries are inconspicuous.

monia cannot be determined, because of the great variation in quantity of peribronchial lymphoid tissue which occurs in the lung of the healthy rat. No tissue was examined from animals that survived the pneumococcic infection for longer than eleven days.

In a few rats, killed after from seven to nine days, resolution was well advanced in the parenchyma of the affected lobe, but plugs of cells and fibrin persisted in the bronchi. In the unresolved portions of the lung the alveoli were fully distended, while in the resolved areas the alveoli were collapsed, containing no air and only a few macrophages and scanty granular débris.

CONTROL EXPERIMENTS

Since in all the experiments concerned primarily with pathogenesis the infecting cultures of pneumococci were suspended in mucin and since in some instances india ink also was added as a tracer, it was necessary to study the effects of these two substances without the addition of pneumococci. Besides these a few experiments were tried with injections of suspensions of pneumococci in saline solution instead of suspensions in mucin. The essential histologic observations are described briefly in the following paragraphs.

Mucin; Mucin and India Ink.—The effects of mucin alone were variable but usually slight, as compared with the effects of mucinous suspensions of virulent pneumococci in mucin. In from one to four hours, little or no difference could be detected either grossly or microscopically between the alterations produced by injections of mucin alone and those produced by mixtures containing bacteria. These alterations consisted first of swelling and proliferation of septal cells and somewhat later of infiltration of neutrophils. On the other hand, in a few cases practically no evidence of irritation could be seen in the area which received the mucin, although the concentration and distribution of the mucin were essentially the same as in the other cases. This leads one to suspect that in some cases the mucin became contaminated with extraneous bacteria which were pushed down from the pharynx or trachea on the end of the tracheal cannula or possibly were already residing in bronchioles and parenchyma. At later periods, up to twelve hours, leukocytic infiltrate increased in density but not in a degree comparable with that of the lungs infected with pneumococci.

With few exceptions the inflammatory reaction was limited to the area of injection. In two cases in which there was fairly extensive confluent lobular and diffuse pneumonia at twenty-four and forty-eight hours, respectively, no bacteria could be demonstrated in the stained sections, and there was a conspicuous preponderance of macrophages in the intra-alveolar exudate. In both of these fibrin was extremely scanty. In a third instance, in which there was an exceptionally extensive exudate, confluent bronchopneumonia of one lobe (the lobe which was inoculated) was noted in a rat killed in twenty-four hours, and in this case numerous small gram-positive cocci resembling streptococci were free in the exudate and within phagocytes. In only four of the twenty-two rats which received mucin alone or mucin and india ink was there any stainable fibrin in the lesions, and in these it was scanty. After twenty-four hours the neutrophils were diminished in number, and macrophages formed the chief element in the exudate. They persisted singly and in small irregular groups for as long as three days after the time of injection. The only animal of this group that was studied histologically after a period of survival longer than three days was killed at six days and showed no traces of inflammation in either lung.

When ink was a part of the injected mixture the macrophages were much more conspicuous, especially in the early stages of development of the lesion, because of the ingestion of particles of carbon. Whether they were actually more numerous is doubtful. The stages up to twenty-four hours were essentially the same as when mucin was injected alone. We made no study of material from animals killed at later periods.

So far as can be determined, the addition of ink to bacterial mixtures does not appreciably affect the extent or course of the disease further than the limitation of the initial lesion owing to the physical properties of the ink. In the later stages the only differences noted are the conspicuous marking of the macrophages by the phagocytosed particles of carbon with which most of them are filled. This does not appear to impair resolution in any way.

Suspensions of Pneumococci in Saline Solution.—In the occasional "takes" observed after intrabronchial insufflation of suspensions of pneumococci in saline solution without mucin the only difference that could be seen at microscopic examination was in the intensity of the inflammatory reaction in the lung, as judged by the quality and quantity of the exudate. In only three of the thirty-five rats that were given 10^{-5} cc. of culture suspended in saline solution was well developed lobar consolidation observed. In one killed at three days the quantity of fibrin was much less than that in the average animal with pneumonia resulting from the usual suspension in mucin. In one of two killed at four days, fibrin was comparatively abundant, and in other respects also the histologic picture was practically identical with that seen in other cases of experimental lobar pneumonia. Two animals that were found dead about twenty-four hours after injection showed early purulent bronchitis, edema of the parenchyma and scanty leukocytic exudate of the parenchyma around the inflamed bronchi. The others that were examined showed various grades of confluent bronchopneumonia in one or both lungs.

Influence of the Type of Pneumococcus.—Nearly all the experiments on the animals of this group were carried out with a type III strain of pneumococci (obtained from Dr. L. Webster), for the reason that this had been used with success in a large number of rats and its virulence for this animal was well known. For the sake of comparing the effects of this strain with those of another well standardized strain, a few rats were given comparable doses (10^{-4} cc. of twenty-four hour bouillon cultures) of a type I strain obtained from Dr. O. H. Robertson. So far as could be judged from a small series of animals, this type I pneumococcus when injected intratracheally in mucin possessed a virulence for rats that was approximately equal to that of the type III strain used. The gross and the microscopic picture were the same. Greater differences were noted in the quantity of fibrin deposited in the involved tissue between individual animals in each series than between animals given injections of different types of pneumococci. The differences therefore must be attributed to varying susceptibility of the animals used and to differences in the distribution of the inoculum rather than to a difference in virulence of the two types of pneumococci used in these experiments.

Influence of Previous Pulmonary Infection.—In an animal as small as the rat it is difficult to determine by fluoroscopy or by roentgenograms the exact site and extent of an inflammatory process, as did Robertson and his associates in their experiments on dogs. For this reason we have not attempted to study the effect of repeated infections in the lungs of rats. However, in one group of animals we observed evidence in several cases of previous inflammation in the form of thickening of the alveolar walls, an increased number of macrophages in the alveoli

and scanty peribronchial and perivascular infiltration of neutrophils, lymphocytes and histiocytes. While in most of these the recent inoculation resulted in diffuse spreading exudative pneumonia, which covered up the older, subsiding process, the pneumonia tended to be less extensive in a given time, and fibrin was distinctly less abundant than in the animals of other groups which had received the same dose and which showed no histologic evidence of previous infection. No instance of spontaneous lobar pneumonia has been observed by us in the material examined. The spontaneous disease observed has been of the nature of chronic bronchitis and focal and "interstitial" pneumonia. No bacteria are seen in microscopic sections in these cases. The predominance of macrophages in practically all cases suggests a subsiding process or a mild chronic inflammation. The occasional occurrence of localized chronic bronchitis associated with bronchiectasis and the accumulation of cellular débris in the dilated bronchi ("Hektoen's abscesses"[8]) appears to have no inhibitory influence on the development of experimental pneumonia, provided most of the inoculum is distributed elsewhere to essentially healthy tissue, as is usually the case. This is probably due to the fact that the diseased bronchi are obstructed by the "abscesses."

The most significant observation in this group of animals which showed histologic evidence of previous bronchopulmonary infection was the relatively low percentage of "takes" as compared with that in the other groups of normal animals.

COMMENT

It is evident from the foregoing description that the developmental stages of experimental pneumonia induced in rats by intrabronchial injections of pneumococci in mucin are closely analogous to the stages of spontaneous pneumonia in human beings described by Loeschcke.[9] There are, of course, differences in the element of time due to differences between the rat and man with regard to metabolism and susceptibility to pulmonary infections. The similarities between the histologic features of experimental pneumonia in dogs, as described by Robertson, Coggeshall and Terrell,[4b,c] and those observed by us in rats are even more striking. The development of the initial exudative lesion in the dog's lung as observed by Robertson is more rapid than in the rat under the conditions of our experiments. This may be explained satisfactorily by the fact that the dose of pneumococci was much greater in the case of the dog. The dose used by Robertson in his studies of pathogenesis was from 0.05 to 0.6 cc., while in ours the dose used was from 0.00001 to 0.0001 cc. Larger doses than this frequently produced fatal lobar pneumonia in the animal in from twenty-four to forty-eight hours. Our experience was identical with Robertson's in that previous sensitization of the lungs was found to be unnecessary. Furthermore, it was not necessary to lower the resistance of the rat by chilling, by injecting morphine sulfate or by other means, unless one includes the light ether anesthesia used to keep the animal quiet during the passage of the tracheal tube.

8. Hektoen, L.: Tr. Chicago Path. Soc. **10**:105, 1916.
9. Loeschcke, H.: Beitr. z. path. Anat. u. z. allg. Path. **86**:201, 1931.

Fibrin appeared at an earlier hour in Robertson's dogs than in our animals. This also was probably due to the administration of a larger dose of bacteria, since the injected mixture in our experiments was found to be incapable of inducing the precipitation of fibrin until after the pneumococci had increased in number by proliferation in the alveoli. This initial lag which preceded the stage of rapid development of the fibrinous exudate and rapid spread of the lesion varied from four to about twelve hours. As a rule the interval was shorter when the larger dose of infecting organisms was introduced and longer with the smaller dose. While we have no means of determining accurately the concentration of pneumococci and their toxic products in a given mass of tissue, the evidence at hand seems to indicate that fibrin does not appear until after the bacteria are present in considerable numbers. The production of large quantities of fibrin must be associated with an irritation of relatively great intensity, since lesions which show large amounts of fibrin in an early stage show also large numbers of erythrocytes in the alveoli. We assume that the pneumococcic toxins cause sufficient damage to the endothelium of the capillaries to render them more permeable than normal, thus permitting blood cells and plasma to escape into the air spaces. This conception seems best to fit the observations made in this series of experiments.

So far as the evidence gleaned from our material bears on the question of how the lesion spreads from one part of the lung to the other, it supports the conception of Loeschcke [9] derived from his morphologic studies of lobar pneumonia in human necropsy material. He concluded that the principal mode of spread of the infecting microorganism is in the edema fluid itself, which, arising in the irritated tissue at the site of the initial focus, is carried from one alveolus to another either through the pores of Cohn or through the wider openings of the atria. The thin edema fluid flows readily from the inflamed area, an area of positive pressure, to uninvolved lung, assisted by the increased negative pressure created during each inspiratory effort. The spread from an infected area to a more dependent area is probably assisted also by gravity. The edema fluid serves as an excellent culture medium for the pneumococci, which are carried with it to healthy tissue, and the organisms immediately begin to proliferate at a rapid rate. Robertson and his associates have stressed the importance of the time factor in accounting for the somewhat puzzling fact that pneumococci apparently can proliferate without hindrance in the edema zone of a spreading pneumonic lesion in an animal with blood showing marked pneumococcidal properties. A certain interval of time is necessary, they explained, for the full opsonizing effect of the serum to take place. The serum alone (of the dog) has no bacteriostatic effect, and the leukocytes have not yet had sufficient time to reach the area of multiplying bacteria. By

the time the leukocytes have reached the site in sufficient numbers, the bacteria and the edema fluid have spread beyond this site, and the cycle is repeated.

In addition to the transportation of pneumococci by the outflowing edema fluid, there is evidence in our material that they may be spread by the active migration of microphages and macrophages, just as carbon particles are carried from one area to another. This mechanism of spread of infection has been supported by the observations of Cunningham and his associates [10] on infections with tubercle bacilli. It is not easy to prove the presence of viable pneumococci within phagocytic cells, since the bacteria seem to lose their characteristic morphology and staining properties soon after phagocytosis has occurred. The loss of ability to retain a gentian violet stain has been generally interpreted as evidence of intracellular digestion and loss of viability, but there is much evidence to the contrary. The intensity of the local inflammatory reaction is frequently out of proportion to the number of stainable bacteria. If dissemination of bacteria by such means actually occurs, it seems likely that the polymorphonuclear leukocyte is the more important agent, since not only is it more actively motile but, being highly sensitive to bacterial toxins and changes in p_H, it disintegrates more quickly than does the macrophage. This mechanism may account also for the frequency with which pneumococci appear in the blood stream in the early stages of pneumonia. Neutrophils are known to migrate more or less freely through the walls of capillaries in either direction at the site of local inflammation, and this has not been demonstrated for macrophages. It does not seem reasonable to assume that free nonmotile bacteria are able to pass through the intact walls of blood capillaries at a time when plasma is passing in the opposite direction, from capillary to alveolus, as is the case in the early stage of pneumonia. The presence of large numbers of cocci in the vessels of the parenchyma early in the evolution of the lesion, which was observed by Robertson and his associates [5e] in the dog, was not duplicated in our experiments on the rat. In fact, during the first few hours after inoculation, when any bacteria were seen they were always in the lumens of alveoli or bronchioles and mixed with mucin.

On the third day the exudate may begin to shrink away from the alveolar walls. The greatest degree of shrinkage occurs in the alveoli which contain the denser fibrinous nets. In alveoli which contain little or no fibrin, no clear spaces between the exudate and the alveolar walls may appear. This factor, as in cases of pneumonia in human beings, varies from place to place and from individual to individual.

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10. Cunningham, R. S.; Sabin, F. R.; Sugiyama, S., and Kindwall, J. A.: Bull. Johns Hopkins Hosp. **37**:231, 1925.

The termination of the lesion in animals which received sublethal doses is identical in all essential features with the termination of lobar pneumonia in human beings by resolution. The first evidence of beginning resolution is a proportional increase of alveolar phagocytes and a corresponding decrease of polymorphonuclear neutrophils and fibrin. Occasionally areas were noted in which fibrin and granular débris constituted practically all the intra-alveolar exudate, without the appearance of many macrophages, but in no case was there any evidence of solution of fibrin before the appearance of macrophages. The occurrence of large numbers of macrophages in any area is always associated with a great reduction or a complete absence of fibrin in that area. It seems reasonable to assume from this circumstance that it is the macrophage and not the neutrophil that is in some way responsible for the disappearance of the fibrinous exudate. The persistence of the fibrinous plugs in the larger bronchi for days after most of the fibrinous exudate has been cleared from the parenchyma is in all probability due to the fact that the macrophages do not reach the lumens of these obstructed bronchi until late in the course of the disease. In these the neutrophils are more or less abundant from the time the exudate first appears in the bronchi, but no evidence of the solution of fibrin (in the bronchi) appears until about the seventh day at the earliest. The fibrinous plug is dissolved from the periphery inward, and the very first evidence of solution is accompanied by the presence of one or more layers of macrophages at the periphery. By the time these appear, the epithelial lining of the bronchus has disappeared in all but occasional small patches, and even these are frequently separated from their basement membrane and are in various stages of disintegration.

In the few rats that survived and were killed at nine and eleven days, restoration of bronchial epithelium was complete. This apparently begins before the exudate has been completely removed from the lumens of the bronchi, since in some cases extremely tall hyperchromatic cells with numerous mitotic figures line partly collapsed bronchi which contain unresolved plugs of exudate. In these cases the parenchyma supplied by the obstructed bronchi is collapsed, even though practically free from exudate. This stage in the process of restoration of the lung to the normal state is, in all probability, analogous to postpneumonic atelectasis (without massive exudation into the pleural cavity) which is so frequently demonstrable by roentgen examination but which is comparatively rarely seen at the necropsy table, since it is a transient stage that occurs only in the successfully resolved condition. Unfortunately our material from this period of resolution is entirely too small to permit a comparative analysis and does not justify the drawing of any general conclusions.

SUMMARY

The lesion in the rat's lung which results from intrabronchial insufflation of pneumococci suspended in mucin usually begins at the base near the posterior diaphragmatic border. The size of the initial lesion is determined by the distribution of the inoculum, and if this is widely distributed the lesion is formed by the coalesence of several foci of edema and leukocytic exudate. After a delay of a few hours, during which time the pneumococci increase in number, the lesion begins to spread rapidly in all directions and continues to spread until arrested by the pleural membrane.

The most important mode of spread of pneumococci from infected to normal parenchyma is by the outflow of edema fluid through the smaller air passages and pores of Cohn. The organisms propagate rapidly in this fluid so long as it is poor in leukocytes. Another probable mode of dissemination is by the active migration of leukocytes from an infected zone to normal tissue after phagocytosis of the micro-organisms.

The earliest cellular response is of the septal cells, followed closely by infiltration of polymophonuclears, which soon predominate in the cellular exudate. Erythrocytes and fibrin regularly constitute a part of the alveolar exudate but vary considerably in their relative concentration. The quantity of fibrin apparently depends on the intensity of the irritation. The first evidence of resolution may appear as early as twenty-four hours after inoculation in cases of mild infection, but seven days or more is required for the complete disappearance of exudate from lungs which have been involved entirely. Shrinkage of the fibrinous exudate in the alveoli usually appears in about three days, resulting in a mosaic appearance comparable to that of fully developed croupous pneumonia in human beings. The stage of resolution is characterized by the presence of large numbers of macrophages. These cells appear to arise largely by the local proliferation of septal cells, and they are chiefly, if not entirely, responsible for the liquefaction of fibrinous exudate. The residual thickening of the alveolar walls after resolution has occurred is in large part due to the increased number of swollen septal cells.

Case Reports

PILONIDAL CYST, SPINA BIFIDA OCCULTA AND BIFID SPINAL CORD

Report of a Case with Review of the Literature

W. B. Hamby, M.D., Buffalo, N. Y.

Anomalies in the midline of the skull and spine due to faulty embryologic fusion of anlagen may take many forms and present bizarre clinical pictures. Complicated abnormalities may occur in the spinal cord, its meninges, the bodies, laminae and spinous processes of the vertebrae and the overlying tissues. A case is presented of reputed familial spina bifida occulta, accompanied by a patch of hair in the lumbar region, a pilonidal cyst, a bony process bridging the spinal canal and an elongated and apparently bifid spinal cord. No previous report of a case has been found in which a similar combination of anomalies was presented. The anomalies are described as they appeared clinically and at operation.

REPORT OF CASE

A white woman, aged 20, was admitted to the Buffalo City Hospital on April 24, 1935. She complained of pain in the lumbosacral area radiating to the right hip and leg, with difficulty in walking, due to stiffness of the right leg. At birth a dimple had been noticed in the midline of the lumbar area, and later a profuse growth of hair occurred in this region. At the age of 11 years the patient had sustained a blow over the lower part of the back, since which time she had suffered a continuous dull aching pain, which had radiated down the right leg for the past three months. During this period the right leg was somewhat spastic and clumsy. She was confined to bed for two weeks prior to admission to the hospital because of extreme pain in the back. There had been no involvement of the sphincters.

There was an interesting family legend that the eldest girl suffered from spina bifida and that the boys did not have the condition, the transmission being through the female side. The patient's grandmother was said to have suffered from a similar lesion, and the patient's baby died at the age of 3 weeks, in 1932, of meningitis following leaking of a spina bifida sac. Except for her mother, the patient's family was in Sweden, and the legend could not be verified. Her mother had no demonstrable evidence of spina bifida, and roentgen examination of her spine revealed no abnormality.

The patient was well developed, with no abnormalities other than those referable to the lesion described. There were a quadrilateral area of hairy growth and moderate lordosis in the midlumbar area (fig. 1). No muscular abnormality was noted in the legs. The right knee jerk was slightly exaggerated, and the ankle jerks and plantar responses were normal. There was anesthesia of the "saddle area," and a band of hypesthesia extended down the backs of both legs. Roentgenograms of the spine (fig. 2) showed the laminae of the third, fourth and

From the Buffalo City Hospital.

fifth lumbar vertebrae and the major portion of the sacrum to be distorted, with failure of fusion in the midline. There was congenital fusion of the bodies of the fourth and fifth lumbar vertebrae.

Operation.—A laminectomy was performed on April 29, 1935, the skin being opened in the midline from the level of the second to that of the fifth lumbar vertebra. On incision of the deep fascia the dome of a tense, firm tumor was

Fig. 1.—Photograph of the patient, demonstrating the patch of hair in the lumbar region.

Fig. 2.—Roentgenogram of the lumbar portion of the spine, showing distortion of the laminae with fusion of the fourth and fifth lumbar vertebrae. The arrow indicates the location of the spur through the canal.

observed protruding upward. It was freed by subperiosteal reflection of muscles from the spinous processes of the third and fifth lumbar vertebrae and removal of the spinous processes. After dissection the tumor (fig. 3) was seen to be roughly S-shaped, the anterior tip being attached to the bone in the midline from about the third to the fourth lumbar vertebra. It was attached to the surrounding tissues by numerous strands that superficially resembled nerves. An incision into

the tumor revealed a thin wall containing fluid under tension and a mass of curly blond hair. It was removed from the periosteum of the underlying bone. The abnormal laminae were removed piecemeal, the dura being exposed. (Because of the abnormal positions of the laminae and their incomplete development, accurate identification of position was impossible, and the levels indicated are estimations only.)

Below the level of the third lumbar vertebra the dural canal apparently turned toward the right and was uncovered in this direction. When the dura was opened, the cord was seen to be much longer than usual; it "coned down" sharply at the second lumbar vertebra, was cylindric for a distance of 2 cm. and then became bifid, separating into two grossly equal parts to surround a bony extension through the canal at the level of the third and fourth lumbar vertebrae. The process was

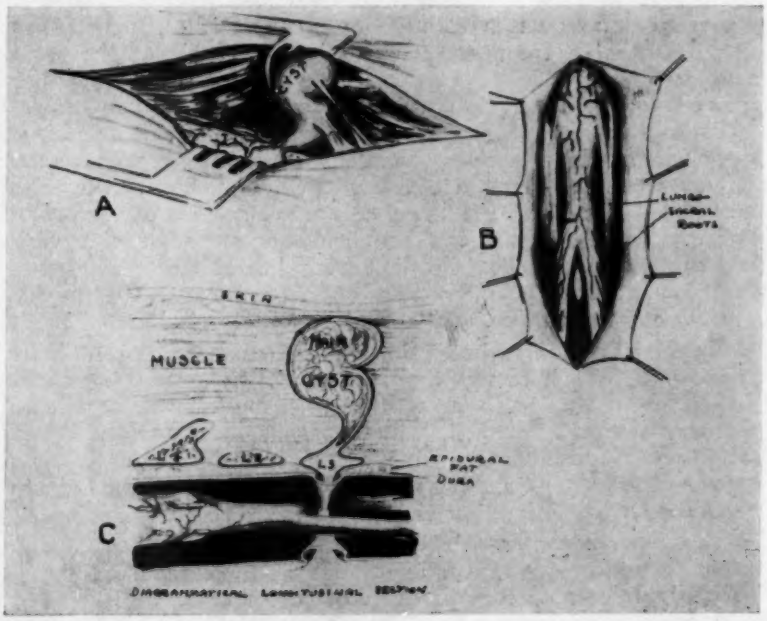

Fig. 3.—Sketches of the lesions revealed at operation. *A* shows the pilonidal cyst in situ; *B*, a view of the bifurcation of the cord at laminectomy, and *C*, a diagrammatic longitudinal section indicating the relation of the lesions.

enclosed in a tubular investment of dura. The canal was widened at this point, and only the dura to the right of the process had been uncovered by the laminectomy. The posterior aspect of this process was the site of attachment of the tip of the pilonidal cyst. On gross examination of the cord, no nerve roots were seen to arise from the cylindric portion. The bifid portions quickly broke up into caudal filaments, the separation into roots beginning on the lateral aspects of the cords.

No other abnormalities were noted, and the incision was closed.

Microscopic examination of the excised tissue revealed a capsule of connective tissue with a lining of stratified squamous epithelium bearing sudoriparous and sebaceous glands and hair follicles.

The patient had an uneventful convalescence, and when she was last seen, on Dec. 3, 1935, she stated that she felt well except for occasional tiring of the back, at which time the right leg sometimes displayed mass movements. The numbness noted prior to operation had cleared, and the reflexes were equal and normal.

COMMENT

Since spina bifida so frequently is associated with varying degrees of maldevelopment of the spinal cord and overlying structures, it is believed to be secondary to faulty development of the neural tube. Keiller [1] stated that any defect in the development of the neural tube is associated with defects of the vertebral canal. That this is not always applicable is indicated in the case reported by Lipschutz,[2] in which the cord was bifid and yet the arachnoid and overlying structures were normal. Moreover, spina bifida occulta probably is not due to this cause, since it is of frequent occurrence and in most of the patients no associated changes in the cord are present.[3] Karlin [4] found that in 54 per cent of normal children spina bifida occulta is demonstrable by roentgen examination. Spina bifida in association with meningocele or myelomeningocele is thought by many to be due to an increase in intracranial pressure during fetal life, preventing fusion of the anlagen of the laminae,[5] but when the meninges are normal this factor is hardly applicable. Dittrich [3] gave an excellent summary of the various skeletal and neurologic complications of spina bifida occulta, with a review of the literature. Von Recklinghausen [6] expressed the belief that it was due to primary aplasia of the skeletal axis.

Heredity.—Various authors [7] have noted cases of spina bifida in members of the same family, and Alpers and Waggoner [7a] expressed the belief that the anomaly is evidence of a tendency to degeneration of the family stock. Brickner,[8] however, stated that spina bifida is not a hereditary phenomenon. In the case reported in this paper, the statements of the patient and her mother are in support of the hereditary transmission of the lesion, but circumstances prevent verification of it.

Associated Anomalies.—Abnormal Length of the Spinal Cord: Abnormal length of the cord is due to failure to escape from the fetal status. Brain [7b] stated that in cases of lumbosacral spina bifida the cord frequently retains its fetal length and extends as low as the sacrum. In a 3 month fetus the cord extends to the tip of the coccyx,

1. Keiller, V. H.: Brain **45**:31, 1922.
2. Lipschutz, B.: Arch. Neurol. & Psychiat. **4**:16, 1920.
3. Dittrich, R. J.: Surg., Gynec. & Obst. **53**:378, 1931.
4. Karlin, I. W.: Am. J. Dis. Child. **49**:125, 1935.
5. (*a*) Hodges, R. M.: Boston M. & S. J. **103**:485, 493 and 544, 1880. (*b*) Humphry: J. Anat. & Physiol. **20**:585, 1886.
6. Von Recklinghausen, F. D.: Virchows Arch. f. path. Anat. **105**:243, 1886.
7. (*a*) Alpers, B. J., and Waggoner, R. W.: Arch. Neurol. & Psychiat. **21**: 47, 1929. (*b*) Brain, W. R.: Diseases of the Nervous System, London, Oxford University Press, 1933, p. 552. (*c*) Mandruzzato, F. A.: Am. J. Surg. **16**:104, 1932. (*d*) Moise, T. S.: Surg., Gynec. & Obst. **42**:394, 1926.
8. Brickner, W. M.: Am. J. M. Sc. **155**:473, 1918.

and as the canal grows in length, the conus gradually migrates up the canal, until at birth it is at the level of the third lumbar vertebra. Since the tip of the cord is attached to the coccyx, it is gradually attenuated into the slender filum terminale.[1]

Double Spinal Cord: Abnormalities of the nerve tissue underlying spina bifida may range in severity from complete rachischisis to the simple enclosure of nerve roots within a myelomeningocele. Doubling of the spinal cord is rarely observed and involves only part of the cord unless the vertebral canal is also double. Dana [9] stated that the condition sometimes occurs in association with spina bifida. Grossly, in the case described in this paper the cord was of abnormal length, with duplication of its terminal portion. Mixter [10] called attention to the fact that the central portion of the cauda equina may be fused into a "single irregular bundle having almost the appearance of a small spinal cord." This bundle of fused roots may be the site of various pathologic processes, such as dermoid cyst, lipoma, etc. Histologic verification of duplication of the cord was not possible in the case reported.

Several cases of duplication of the cord have been reported, and in seven instances the bifurcation also embraced bands that incompletely divided the canal vertically.

Altschul [11] reported a case in which the spinal cord was furrowed by three longitudinal fissures that so deepened as to split the cord into three irregular bundles, separated from one another by pia, the triplicate cord being enclosed in a single dural sheath. At the level of the fifth dorsal segment the bundles coalesced to form a single cord. He attributed the lesion to splitting of the medullary plate or rolling in of its edges, with subsequent separation into bundles.

Lipschutz [2] reported a case in a man, aged 35, in whom the vertebrae, the tissues of the back and the skin were normal. The dura and arachnoid appeared normal, but when the cord was opened, it was observed to bifurcate at the level of the eleventh dorsal vertebra, the two cords ending at the upper border of the first sacral vertebra. The conus of each cord was well formed, but at the level of the third sacral vertebra they united to form a large filum terminale, attached to the dorsal surface of the coccyx. At the level of the twelfth dorsal vertebra an anteroposteriorly directed band of dura, shaped like an hour-glass, projected between the two cords. The author expressed the belief that the dural band was the etiologic factor in the splitting of the cord, but he was unable to explain the mechanism. This case resembles the one presented in this paper as to the elongation of the cord, the division of the cord into two longitudinal portions and the interposition of a dural partition between the two portions. Branching or duplication of the neural canal may exist, a case of such a condition having been reported by Radasch.[12]

Schenck [13] reported the case of a 5 month fetus in which the spinal cord was in the form of a plate, the ventral sulcus of which was enlarged dorsad, causing

9. Dana, C. L.: Text-Book of Nervous Diseases, ed. 10, New York, William Wood & Company, 1925, p. 228.

10. Mixter, W. J., in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 12, chap. 3, p. 90.

11. Altschul, R.: Virchows Arch. f. path. Anat. **271**:45, 1929.

12. Radasch, H. E.: Anat. Rec. **15**:57, 1918.

13. Schenk, V. W. D.: Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:369, 1933.

duplication of the cord with two medullary canals. Acrania and rachischisis were also present.

Smith [14] reported a case of a 5 day old infant with a meningocele between the level of the second and that of the fifth dorsal vertebra; palpation of the tumor revealed a firm bony spur projecting upward from the vertebral column. When the lesion was opened, the laminae of the second to the fifth dorsal vertebra were noted to be absent, and from the body of the fourth dorsal vertebra projected upward a spur of bone, 3 by 1 by 0.5 cm., with a knobbed head, to which was attached the dural roof of the meningocele. The cord divided to pass around the spicule, reunited below it and terminated at the level of the second lumbar vertebra. Microscopic sections of the cord above and below the lesion showed normal structure. Above and below the defect the dural and arachnoid sheaths were normal. The muscular development of the body was normal, but this does not depend on the development of the cord, since the muscles can develop and the spinal nerves be present even when the cord and brain fail to develop.[15] In this case hydrocephalus and atresia of the anus were also exhibited.

Weber [16] reported the results of postmortem examination of a man, aged 51, with combined degeneration of the cord. He observed a process 1 cm. in diameter and 6 cm. in length, branching from the left side of the cord, 7.5 cm. above the terminal part of the conus. It tapered to a point and bore no nerve roots. Histologic examination revealed that it was a fairly well developed duplicate spinal cord with a central canal. It showed marked signs of combined degeneration, as did the main portion of the cord.

Humphry [5b] reported six cases that he had observed in and around London, in which spina bifida occurred with bony projections from the bodies of the vertebrae into the vertebral canal. In all except case 3 the spinal cord was described as passing in two portions around the process which bisected the canal.

Fürstner and Zacher [17] reported a case of apparent partial duplication of the cord in the lower part of the dorsal region, but Van Gieson [18] expressed the belief that in this case and in several others previously reported the condition was due to trauma of the cord at the time of its removal from the canal.

Weil [19] reported a case in which the spinal canal was divided by an anteroposteriorly directed bony process, with spina bifida and gross distortion of the spine. Since he examined only the skeleton, the status of the cord is unknown.

Superficial Abnormalities: The tissues superficial to spina bifida may harbor many abnormal structures. This is especially true in the sacrococcygeal area, because of the multiplicity of complex embryologic changes that occur there. Bucy and Haymond [20] reported a case of a teratoma connected by a stalk to the intraspinal contents. This condition is rare, as their analysis of the literature revealed. Lipoma is observed fairly frequently. Moise [7d] reported a case in which

14. Smith, E.: J. M. Research. **38**:479, 1918.
15. Dittrich, R. J.: Arch. Path. **10**:395, 1930. Mandruzzato.[7e]
16. Weber, F. P.: Brit. M. J. **1**:1106, 1928.
17. Fürstner and Zacher: Arch. f. Psychiat. **12**:373, 1881.
18. Van Gieson, I.: New York M. J. **56**:337, 365 and 421, 1892.
19. Weil, S.: Arch. f. klin. Chir. **170**:100, 1932.
20. Bucy, P. C., and Haymond, H. E.: Am. J. Path. **8**:339, 1932.

meningitis developed in the presence of a draining sinus leading through an imperfectly closed sacrum.

Several theories have been developed to explain the occurrence of pilonidal cysts and sinuses. Hodges,[5a] who gave the lesion its name pilonidal (*pilus*, a hair; *nidus*, a nest), expressed the belief that a congenital dimple must exist in the presence of an abundant pilose development. As the hair is fragmented by friction with the clothing, it fills the dimple, with the addition of dirt and products of maceration of the skin, thus producing an irritated lesion, which he noted most frequently in men of unclean bodily habits.

Mallory,[21] in studying nineteen cases of pilonidal sinus, in the majority of which infection occurred, investigated the matter on an embryologic basis and concluded that the lesion arose in remnants of the normally obliterated medullary canal. Oehlecker [22] confirmed these observations, thus giving an embryologic explanation for epithelium-lined spaces occurring in the sacrococcygeal area, whether or not they communicate with the skin. Fox [23] showed that in the fetus invagination of the skin in this region is not uncommon and that the cutaneous appendages, viz., the sebaceous and sudoriparous glands and hair follicles, may accompany them. He reasoned that such invaginations could be the origin of the pilonidal sinus and dermoid cyst, while the vestiges of the medullary canal could give origin to the tumor with neuroblastic inclusions. This may explain why Glenn [24] found by roentgen examination only two examples of spina bifida occulta in nineteen cases of pilonidal sinus. Stone [25] suggested that these invaginations may be the phylogenetic representation of the preen gland which develops so prominently in birds.

In the 12 mm. embryo, Oehlecker [22] identified the caudal filament, a prolongation of connective tissue from the caudal vertebrae. As the caudal vertebrae grow downward the skin is displaced upward with the attached tip of the caudal filament. In a fetus of from 4 to 5 months, the skin originally overlying the coccyx is drawn up to the level of from the third to the fourth caudal vertebra. The pull of the caudal ligament on the skin causes dimpling. In a summary of the embryologic data, Gage [26] concluded that a pilonidal sinus arises from anomalous development of the medullary canal and that coccygeal dimples result from disturbances in development of the coccygeal ligament and thus are never connected with the medullary canal. Pilonidal sinuses are of several types, depending on the portion of the canal that fails to be obliterated.

These theories may explain pilonidal sinus and cyst of the sacrococcygeal region but seem inadequate to explain these anomalies in the lumbar, dorsal and cervical levels of the cord, well removed from the vicinity of the posterior neuropore. Walker and Bucy [27] reported two

21. Mallory, F. B.: Am. J. M. Sc. **103**:263, 1892.
22. Oehlecker, F.: Deutsche Ztschr. f. Chir. **197**:262, 1926.
23. Fox, S. L.: Surg., Gynec. & Obst. **60**:137, 1935.
24. Glenn, Frank: New England J. Med. **207**:544, 1932.
25. Stone, H. B.: Ann. Surg. **94**:317, 1931.
26. Gage, M.: Arch. Surg. **31**:175, 1935.
27. Walker, A. E., and Bucy, P. C.: Brain **57**:401, 1934.

cases of subdural abscess communicating with the skin through a congenital sinus in the presence of spina bifida and mentioned six cases of subdural dermoid communicating with the skin. The authors expressed the belief that these lesions did not result from failure of closure of the medullary canal, as this would limit their occurrence to the sacrococcygeal area and would fail to explain the lesions occurring in the lumbar, dorsal or cervical region. They visualized a connection remaining between the skin of the back and the meninges, which is drawn into a narrow tube as the dorsal tissues increase in thickness.

In the patient whose case is described, a dimple appeared in the midline of the lumbar area at birth, yet at operation the cyst was so confined under the deep fascia that its dome protruded as though under pressure when the fascia was incised. The cyst was not connected in any way with the dura but was attached to the bony spur that had protruded through an invagination in the dural canal. This may suggest that the extramedullary anomaly was primary, although such a condition does not seem likely in view of the sequence of development of the medullary tube and its coverings. That there are profound embryologic forces at work in the production of these lesions is evidenced by the diverse and widespread anomalies observed in some cases.

SUMMARY

A case is described of a young woman with a patch of hair in the lumbar region and spina bifida occulta complicated by (*a*) abnormal lengthening of the spinal cord, (*b*) apparent bifurcation of the lower portion of the spinal cord, (*c*) division of the spinal canal by a bony process and (*d*) a pilonidal cyst not communicating with the skin. The literature is reviewed, and the existing theories are analyzed for an explanation of the development of the lesion. All phases of the complicated lesion are not adequately explained.

MALIGNANT ENDOCARDITIS DUE TO BACILLUS PYOCYANEUS

J. J. KEARNS, M.D., CHICAGO

The case reported in this paper is unusual in that it illustrates the combined effect of physical debility caused by addiction to the use of drugs and the pathogenicity of an organism the virulence of which for man is ordinarily low. The portal of entry was apparently the skin at the site of numerous punctures with the hypodermic needle, as evidenced by the presence of partly healed abscesses.

REPORT OF A CASE

History.—At the time he was admitted to the hospital, a white man, aged about 35, complained of loss of appetite, weakness, fever, chilly sensation, shortness of breath, cough and painful swelling of the left forearm. He ascribed the onset of symptoms to a thorough drenching and chilling during a rain-storm. On awakening the following morning he "felt sick all over." Despite this he worked as hostler at a race-track for a few days but finally had to give up because of weakness, which, despite rest, had become more marked. During the day he felt chilly, and during the night, feverish. Shortness of breath had become progressively more marked for ten days prior to admission. The cough had been productive, but the sputum was not blood-stained, nor was there pain in the chest. The swelling of the left forearm had increased since its appearance four days before and finally ruptured spontaneously just before the patient's admission to the hospital, discharging foul, gray-yellow pus. The patient stated that he had had typhoid and influenza during 1918. He said he had never suffered from venereal disease. He had been an addict to the use of heroin for several years and had used hypodermic sets employed by others without sterilization. However, he stated that he had not used heroin during the past several weeks.

Examination.—The rectal temperature was 102.4 F., the pulse rate 120 and the respiratory rate 24. The tongue was coated, brown and beefy; there was considerable dental caries, and the throat was glazed and dusky red. The heart rate was rapid and regular; the size of the heart was not increased, and there was a systolic murmur over the apex, which was not transmitted. Resonance was diminished on both sides of the chest, and râles were audible in various places, being most marked in the base of the lungs posteriorly. Examination of the abdomen revealed distention, diffuse tenderness, tympanism and exaggeration of the peristaltic sounds. On the dorsum of the left forearm, just above the wrist, there was an indurated red area from which a small amount of foul pus escaped. In the skin of the left arm just above the elbow was a recent scar.

The white cell count was 6,000. The urine gave negative reactions for albumin, sugar, acetone and bile. Cultures of the blood and urine taken the day after admission gave a pure growth of Bacillus pyocyaneus. The patient's serum agglutinated typhoid bacilli in dilutions as high as 1:1,280. Repeated cultures of the

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From the Pathological Laboratory of the Cook County Hospital, Dr. R. H. Jaffé, Director, and the Coroner's Office.

blood, urine and feces were negative for typhoid bacilli, but from cultures of the blood and urine B. pyocyaneus was again obtained. Castellani's absorption test with the isolated strain of B. pyocyaneus proved that the positive Widal reaction was of no significance. Seven days after admission the red cell count was 2,400,000, the white cell count 8,000 and the hemoglobin concentration 55 per cent. No malaria Plasmodia were observed.

Diagnosis.—The first diagnosis was typhoid. Later, malaria and miliary tuberculosis were considered. After the blood culture became positive for B. pyocyaneus, the diagnosis of pyocyaneus septicemia was made.

Course of Illness.—For several days a considerable amount of pus was drained from the abscess in the left forearm. Fifteen days after the patient's admission the rectal temperature was 102.8 F., the pulse rate 120 and the respiratory rate 40. Death occurred eighteen days after admission to the hospital and approximately six weeks after the onset of the condition.

Observations at Autopsy.—The conjunctivae and skin were icteric, and there were minute hemorrhagic extravasations in the palpebral conjunctivae, buccal mucosa and skin of the face, neck, trunk and extremities. There were induration and pale blue-red discoloration of the skin over the basilic and cephalic veins of both forearms. Innumerable punctate, pale blue marks occurred in the skin on the anterior and lateral aspects of the left arm. Two gaping defects in the skin exposed the underlying fascia: One, in the middle of the left arm, measured 1.5 by 0.6 cm., and the other, in the left forearm at the level of the middle and lower thirds, measured 1 by 0.6 cm.; both occurred on the lateral aspect of the arm.

The pleural surfaces were smooth. Both lungs contained granular purple-red areas of consolidation. The heart weighed 350 Gm. The wall of the left ventricle measured 18 mm. at the base, and the corresponding part of the right ventricle measured 4 mm. The myocardium was dusky red-brown and moderately firm. The chordae tendineae, papillary muscles and calumnae carneae were thickened. The mitral cusps were thickened, and the auricular surface of the free margins contained a few warty, semifirm excrescences the size of a pinhead. The ventricular surface of the free margin of the aortic leaflets was covered with firmly adherent cauliflower-like, purplish-gray to purplish-red masses, measuring as much as 11 mm. in the greatest diameter. The tricuspid and pulmonary valves showed no changes.

The liver weighed 2,000 Gm., and the consistency was less firm than normal. The spleen weighed 550 Gm. and contained several recent anemic infarcts, which measured as much as 20 mm. in the greatest diameter. The adrenals together weighed 20 Gm. The pancreas weighed 100 Gm. The kidneys together weighed 395 Gm., and the left kidney contained a recent anemic infarct, which measured 17 by 20 mm.

The scalp and cranial bones showed no abnormal changes. The leptomeninges over the anterior half of the cerebrum were slightly thickened. The brain showed hyperemia and edema.

Microscopic Observations.—Examination showed that the leaflets of the aortic valve were transformed into a structureless, necrotic material, the free surfaces of which were irregularly scalloped. The necrotic tissue showed ill defined outlines of necrotic cells, some of which appeared to be very large. Throughout the necrotic tissue numerous slender bacilli were arranged in groups and short chains.

Toward the free surface the bacteria became very numerous, and on the free surface they formed a uniform dense mass in which the bacteria were seen protruding over the surface and were intimately mixed with the structureless homogeneous, oxyphilic material. The bacterial masses were covered with a layer of mononuclear and polymorphonuclear cells and with erythrocytes. Many of the mononuclear cells contained bacilli, which were often so numerous as to

Section of the aortic valve fixed in Zenker's fluid and formaldehyde; Giemsa stain; × 900.

obscure the nuclei. No bacteria could be detected in the polymorphonuclear leukocytes. At the point where the leaflet is attached to the aortic ring there was a small triangular area, in the region of which the cellular structures were better preserved. In this area edematous connective tissue was observed, the meshes of which were filled with large mononuclear cells, containing ample cytoplasm, and polymorphonuclear leukocytes. In the adjacent portion of the aorta

the intima was necrotic and contained many groups of bacilli. The mesothelium of the epicardium was swollen and prominent. On the intima of the pulmonary artery slightly above the valve there was a circumscribed area, in the region of which the intima was swollen, thickened, of increased cellularity and covered with clumps of bacteria. The base of the mitral leaflets showed a slight increase in vascularity and cellularity. In sections stained with the Gram-Weigert method no bacteria could be detected, while in the Giemsa sections the bacteria were distinct, assuming a deep blue.

The fibers of the myocardium were slightly increased in thickness; the striations were fairly distinct, and about the nuclei there was a small amount of pale yellow pigment. The capillaries were slightly congested, and the connective tissue about the larger vessels was edematous, with loosely scattered small round cells and mononuclear cells. In the endocardium were small collections of lymphocytes.

The liver cells were well preserved and contained brownish pigment granules. The Kupffer cells were markedly swollen and often desquamated; the cytoplasm was vacuolated, and some of the cells contained small pigment granules in the cytoplasmic septums between the vacuoles. The periportal tissue was loosely infiltrated with round cells.

Underneath the capsule of the kidney were small focal areas of atrophy of the parenchyma. Outside these areas the renal structure was well preserved.

The sinuses of an axillary lymph node were dilated and contained swollen, desquamated endothelial cells, many of which were filled with brownish pigment granules.

REVIEW OF THE LITERATURE

A review of the literature reveals that malignant endocarditis caused by B. pyocyaneus is rare. In a case reported by Büngeler [1] the condition was apparently due to B. pyocyaneus. A man, aged 65, seven years prior to his final illness had had erysipelas in association with endocarditis, which resulted in mitral insufficiency. During his final illness the patient received injections of living saprophytic organisms in the treatment of a nervous disease. The exact composition of the vaccine was not given, except that it contained B. pyocyaneus in addition to other organisms. Septicemia developed, which terminated in death in about three weeks. At autopsy deformity of the mitral valve and ulcerative vegetative endocarditis, with a broad perforation of the cusp, were observed. There were focal necrosis of the myocardium, multiple small abscesses of the kidney and icterus and hemosiderosis of the liver. No reference was made to the histologic changes in the heart valves or in the myocardium. Cultures from the spleen revealed Bacillus proteus, B. pyocyaneus and gram-positive hemolytic streptococci, which were not pathogenic for mice. B. pyocyaneus was not observed in the cultures of the blood.

Thayer's case [2] occurred in the course of an epidemic of pyocyaneus infection with intestinal manifestations. The lesions were similar to those occurring in rather acute vegetative endocarditis. The patient, a woman of 42, died after an illness of from three to four weeks, which presented the features of acute dysenteric colitis. Necropsy revealed, in addition to other extensive lesions, a few minute vegetations on the posterior leaflet of the mitral valve and a clump of larger, fresh,

1. Büngeler, W.: Frankfurt. Ztschr. f. Path. **35**:428, 1927.
2. Thayer, W. S.: Edinburgh M. J. **38**:237, 1931.

fibrinous masses on the free edge of the anterior leaflet. Cultures of material taken from the mitral vegetations, peritoneum, intestinal ulcers and ovarian abscess yielded pure growths of B. pyocyaneus. Bacterioscopically, both short, thick and long, slender bacilli were seen in the endocardial vegetations. This is the type of organism which was observed in the leaflets in my specimen.

SUMMARY

A case of malignant endocarditis due to B. pyocyaneus is reported in a debilitated person who was addicted to the use of drugs. The condition apparently followed cutaneous abscesses at the point of injection of the drug. The essential feature was the transformation of the cardiac valve into necrotic granulation tissue, which harbored enormous numbers of the bacteria. By direct extension the inflammation had traveled upward into the aorta, and there was also focal endarteritis of the pulmonary artery, which could be observed only on microscopic examination. The reports of only two other cases of endocarditis due to B. pyocyaneus could be found in the literature.

Laboratory Methods and Technical Notes

AN IMPROVED METHOD OF FRAMING WATCH GLASS MUSEUM SPECIMENS

C. L. Davis, D.V.M., Denver

Day [1] in 1913 described an improved method for mounting a museum specimen under a watch glass. This method, although used in Europe for many years, was not placed on record and references to the method were not available in literature until Day described the technic. Since that time many institutions have employed this scheme of displaying pathologic specimens.

In utilizing this method, it is of paramount importance that the operator follow the described technic in every detail to obtain the desired results. The greatest difficulty experienced by some who have tried this type of mounting appears to be in the removal of the imprisoned air in the tissues before mounting and in the prevention of air from getting into the fluid surrounding the specimen after sealing. To remove the air in the tissues the use of a suitable vacuum desiccator and the application of a negative pressure of from 20 to 25 inches (50.8 to 63.5 cm.) of mercury for one-half hour are emphasized. To reduce the danger of air getting into the specimen after sealing, two measures are of prime importance, namely, getting a perfect ground edge on the watch glass and using a suitable asphaltum for sealing the joint between the two glasses. The selection of an asphaltum that does not become too hard and brittle after cooling is desirable since cracking and chipping of brittle asphaltum may occur in trimming and handling, thus permitting air to get under the watch glass and into the specimen. For sealing purposes, one may use an asphaltum compound used in sealing wet storage batteries. This compound, although somewhat soft and sticky after cooling, is not affected by atmospheric changes, is more pliable than ordinary commercial asphaltum and does not chip or crack (fig. 1*f*). By observing the procedure outlined, I have experienced little difficulty with air bubbles in the preparation of about one hundred and fifty mounts. Those preparing mounts in humid sections of the country occasionally are troubled with the formation of molds in their preserving fluids. Day suggested boiling the final preserving fluid for one or two minutes over an open flame to drive out the air bubbles in the fluid and also to prevent the subsequent formation of molds. In addition to this procedure, one may add a small crystal of thymol to the fluid before sealing as an added precaution against the formation of molds.

In framing the mounts according to Day's method, I felt that too much time was expended in preparing each specimen and devised a method of framing that not only makes it possible to relieve the operator of this burden but at the same time eliminates the use of glue, simplifying remounting of a specimen when this is necessary.

From the Pathological Division, Bureau of Animal Industry, U. S. Department of Agriculture.

1. Day, L. E.: J. Am. Vet. M. A. **44**:66, 1913-1914.

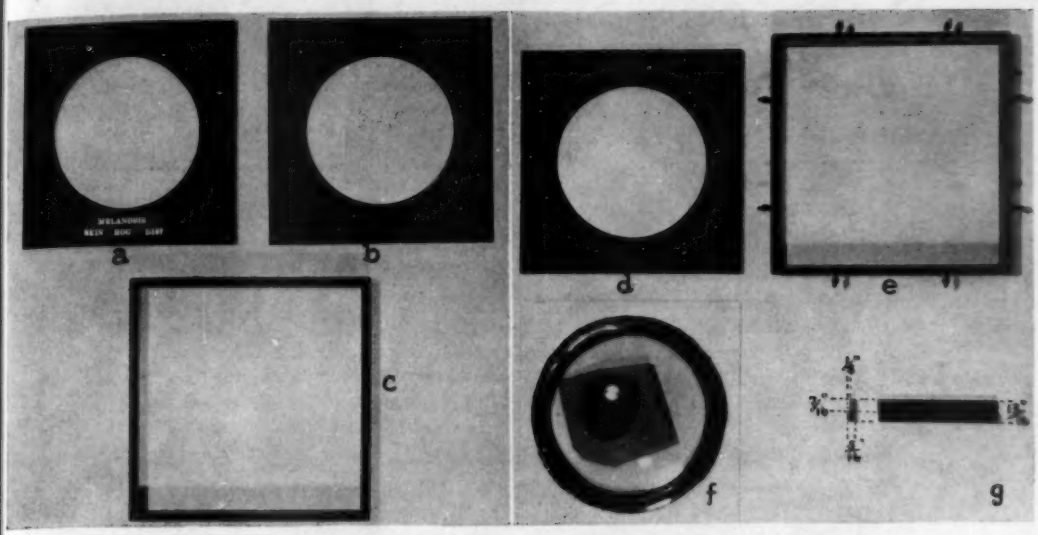

Fig. 1.—In the illustration (*a*) indicates front panel with a 5¼ inch opening; (*b*) back panel with a 5¼ inch opening; (*c*) 8 inch square frame; (*d*) back side of the front panel, showing a ⅞ inch bevel; (*e*) back of the frame, showing the position of the turn buttons; (*f*) specimen under the watch glass, showing the asphaltum seal; (*g*) molding and cross-section, showing the dimensions. The molding is 5/16 inch wide, 13/16 inch high, with one-half round top. The rabbet is 7/16 inch deep and ⅛ inch wide.

Fig. 2.—Front view of the completed mount.

TECHNIC

The frame is constructed of a special picture frame molding and is 8 inches (20.32 cm.) square. The molding is 5/16 inch (0.80 cm.) wide and 13/16 inch (2.08 cm.) high, and has a one-half round top (fig. 1 *C*). The rabbet is 7/16 inch (1.12 cm.) deep and 1/8 inch (0.32 cm.) wide (fig. 1 *g*). The frame is glued and joined. The front panel is a piece of Masonite quarter board (wood fiber board) 7 7/8 inches (20 cm.) square and 1/4 inch (0.64 cm.) thick. An opening 5 1/4 inches (13.34 cm.) in diameter is cut in the panel (fig. 1*a*). A 7/8 inch (2.24 cm.) bevel is then cut on a shaper, using a special knife (fig. 1*d*). The back panel is made of mat board 8 inches (20.32 cm.) square and 1/16 inch (0.16 cm.) thick, with an opening 5 1/4 inches (13.34 cm.) in diameter (fig. 1*b*), which is fastened in with small turn buttons with 1/4 no. 1 flat-head screws (fig. 1*e*). The frame and panels are finished all over with flat black paint. The diagnosis label consists of gold letters stenciled on smooth black leather or leatherette. This is glued on the face panel.

Since facilities for cutting the parts for framing are not available in this laboratory, a contract has been entered into with a local picture-framing concern to furnish the parts and do the framing. The total charge for the completed specimen (fig. 2), including the cost of the plate and watch glass, amounts to about the same as Day's method did. Institutions equipped with carpenter facilities can reduce the cost of framing considerably.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—The Medical Research Council in England has appointed Sir Patrick Laidlow deputy director of the National Institute for Medical Research and head of the department of pathology and bacteriology, in succession to the late Captain S. R. Douglas.

Kenneth F. Maxcy, professor of preventive medicine and bacteriology in the University of Virginia, has been appointed professor of preventive medicine and public health in the University of Minnesota, where he succeeds Harold S. Diehl, who has been appointed dean of the medical sciences.

Frank Fremont-Smith, assistant professor of neuropathology in Harvard University Medical School, has been placed in charge of the medical division of the Josiah Macy Jr., Foundation.

J. G. Fitz-Gerald, of the University of Toronto, will make a study on behalf of the Rockefeller Foundation of the methods of teaching preventive medicine to undergraduates in medical schools.

Sir Robert Muir will retire next September from the chair of pathology in the University of Glasgow, which he has held since 1900.

Eugene Markley Landis, assistant professor of medicine in the University of Pennsylvania, has been awarded the Phillips Memorial Medal of the American College of Physicians in recognition of his work on capillary physiology.

William Thalhimer, until recently director of the Nelson Morris Institute of Michael Reese Hospital, Chicago, is now director of the newly organized Manhattan Convalescent Serum Laboratory, which has been established to function in cooperation with the department of health of New York City.

The honorary degree of doctor of medicine has been conferred by the University of California on Karl F. Meyer, director of the Hooper Foundation for Medical Research.

The two hundred and fifty-thousandth Bausch and Lomb microscope was awarded to F. G. Novy, professor of bacteriology in the University of Michigan, at the meeting of the American Association for the Advancement of Science in Rochester, N. Y., on June 18.

Society News.—William H. Woglom has been elected president; James Ewing, vice president, and Millard C. Marsh, secretary-treasurer, of the American Association for Cancer Research.

Alphonse R. Dochez has been elected president; C. Phillip Miller, vice president, and Shields Warren, secretary-treasurer, of the American Society for Experimental Pathology. The next meeting of the society will be held in Memphis, Tenn., on April 21 to 24, 1937.

The American Association of Pathologists and Bacteriologists has elected N. C. Foote president, E. B. McKinley vice president, F. B. Mallory treasurer and H. T. Karsner secretary. The next meeting will be held at Northwestern University Medical School, Chicago, on March 25 and 26, 1937. The topic for special discussion will be the genesis of tumors.

Forthcoming Cancer Institute at Madison, Wis.—A cancer institute will be held at Madison by the University of Wisconsin Medical School under the auspices of the Alumni Research Foundation on Sept. 7 to 9, 1936. All interested persons are invited to attend. The program will be furnished on request addressed to the dean of the medical school.

Medical Museum in Rochester, N. Y.—In the Museum of Arts and Sciences it is proposed to establish a medical unit under the auspices of the Rochester Academy of Medicine. The historical, artistic and scientific aspects of medicine will be illustrated by both permanent and changeable exhibits.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Intestinal Flora of Monkeys and Dogs During Digestion and Following the Direct Introduction of Food Substances into the Cecum and into Isolated Segments of Bowel. E. Petran, J. Infect. Dis. **57**:296, 1935.

Attempts have been made to alter the relationships of bacteria in the colon and in isolated segments of the large intestine by changing the nutritional environment. Three dogs and one monkey with cecal fistulas, one monkey with an iliac fistula, two monkeys with segments of the large intestine isolated, and one dog with a biliary fistula were used in this study. The organism which outnumbered all others in the intestinal contents (as determined by the methods used in these experiments) was isolated and compared as to numbers with Bacterium coli and in some experiments with Streptococcus, Lactobacillus acidophilus and spore-forming anaerobes.

In the dogs and monkeys the bacterial relationships in the ascending colon were quite constant and were not appreciably altered during the digestive period by the incoming material from the small intestine.

The intracecal injection of dextrose, lactose, peptone and bile (separately) was without noticeable effect on the numbers and relationships of organisms present in the colon. Feeding a diet exclusively of liver to two monkeys caused a great increase in the numbers of sporulating anaerobes in the intestinal contents of one of the animals. In these monkeys, the oral administration of lactose markedly stimulated the growth of L. acidophilus in the large intestine.

The exclusion of bile from the intestine of a dog did not affect the flora of the large bowel.

In two monkeys the flora of isolated segments of the colon was not significantly changed by the injection of bread and milk or lactose in these segments.

From the Author's Summary.

A Lymphatic Connection Between the Gallbladder and the Liver. R. W. Bartlett, G. Crile Jr. and E. A. Graham, Surg., Gynec. & Obst. **61**:363, 1935.

Satisfactory retrograde injections of prussian blue into the lymphatic vessels of the gallbladder were accomplished in the cat after first rendering the valves of these vessels incompetent by preliminary ligation of the thoracic duct with resultant dilatation of all abdominal lymphatics. The dye thus injected was found repeatedly to have passed into the adjacent liver tissue and there to be located in endothelium-lined vessels in the portal spaces. The evidence obtained seems to substantiate the earlier work of Sudler in demonstrating the existence of an intimate lymphatic anastomosis between the gallbladder and the liver. While the experiments showed the transportation of the dye only into the liver immediately adjacent to the gallbladder it seems reasonable to suppose that the connection is more extensive than this. The experiments lend support to the idea that in at least some cases in man there is a lymphatic transport of infection from the gallbladder to the liver.

Warren C. Hunter.

PEPTIC ULCER. E. E. BLANCK, Surg., Gynec. & Obst. **61**:481, 1935.

Previous experimental work has indicated that exclusion of the bile by any one of several methods is instrumental in inducing gastric and duodenal ulceration. The purpose of the present study was to show that the loss of bile was of paramount importance as an ulcerogenic agent. By means of a biliary fistula bile was collected externally. In one series of dogs biliary depletion was allowed to take place, while in another group the fresh bile was fed back to the animals. In the first group gross and microscopic examination of the stomach revealed progressive atrophy of the glandular elements, leading to what Blanck terms "atrophic gastritis." Progressive changes took place on the intestinal side of the pyloric ring as well and were here manifested by a continual loss of tissue leading eventually to true peptic ulceration. By incorporating fresh bile with the food both peptic ulcers and inflammatory changes could be prevented. WARREN C. HUNTER.

EXPERIMENTAL CHOLESTEROSIS OF THE GALLBLADDER. L. M. ROUSSELOT and L. BAUMAN, Surg., Gynec. & Obst. **61**:585, 1935.

Dogs were used. A 0.2 per cent cholesterol solution in a 4 per cent solution of conjugated bile salts was placed in the gallbladder. Within twenty-four hours there was consistently an average loss of 50 per cent of the lipoid. There was an increase in the cholesterol ester in the wall of the gallbladder but no demonstrable increase in the free cholesterol. Grossly in all cases the gallbladder presented a condition closely resembling the picture of human cholesterosis. Under the conditions outlined cholesterol appears to be absorbed by the mucous membrane of the gallbladder.

WARREN C. HUNTER.

THE MANNER IN WHICH NECROSIS ARISES IN THE FOWL'S COMB UNDER ERGOT POISONING. T. LEWIS, Clin. Sc. **2**:43, 1935.

Gangrene of the hen's comb can be produced regularly by day to day injections of 10 mg. of ergotoxine into the breast muscles. A constriction of the arteries, which is unrelieved by relaxing vasoconstrictor tone or by local warming, is thereby maintained and, though a little flow of blood continues, serious nutritional changes occur by the end of a few days. The endothelium of the vessel suffers, plasma is lost, and stasis occurs in the capillaries; clotting follows in central vessels, which are by this time dilated, and necrosis is determined. All these changes can be produced within a few days by mechanically impeding the blood flow to the comb. Vascular spasm in ergot poisoning does not arrest the circulation and so does not cause gangrene directly. The spasm profoundly slows the blood stream and leads to the secondary changes in the vessels described; these are responsible for the arrest of blood flow, which in turn results in death of tissues.

FROM THE AUTHOR'S SUMMARY.

THE LOCALIZATION OF RESPONSE TO ESTROGENIC COMPOUNDS IN THE ORGANS OF MALE MICE. HAROLD BURROWS, J. Path. & Bact. **41**:423, 1935.

The specific action of the estrogenic substance and certain allied compounds is confined to organs which *(a)* in some way serve the purpose of reproduction or *(b)* are morphologically though not otherwise associated with reproduction (e. g., male mamma) or (*c*) are embryologic representatives of the reproductive system (e. g., possible remnants of Müller's duct in the male). The epithelial changes induced by the estrogenic compounds pass through definite successive stages, namely, arrest of function, hyperplasia and metaplasia, with ultimate keritinization and suppuration. Gradients of susceptibility to the estrogenic compounds are seen. Vestigial cysts, if present, are first affected and next the coagulating glands, seminal vesicles and prostate in that order. When the supply of estrogenic substance ceases, recovery in these organs takes place in the reverse order of their susceptibility. In the coagulating glands, seminal vesicles and prostate the metaplasia commences at

definite foci from which it spreads through the glands. Recovery on cessation of the supply of estrogenic substance takes place in the reverse order. Suppuration is a sequel to keratinizing metaplasia; it occurs most readily in those structures which are the slowest to undergo metaplasia and least readily in those which respond earliest to the estrogenic compounds.

From the Author's Summary.

The Method of Choice in the Study of Bile Pressure in the Bile Ducts. J. Bottin, Arch. internat. de méd. expér. **10**:205, 1935.

To study biliary secretion in the dog satisfactorily, the animal must be nonanesthetized and either standing erect or resting in a normal position; it must be healthy and receiving as nearly normal a diet as is possible. The use of the simple gallbladder or bile duct cannula is to be avoided since it introduces the element of biliary obstruction. Intubation of the common bile duct following the method of Rous and MacMaster is likewise objectionable. A more physiologic method is proposed in which the common bile duct is made to empty on the surface of the body, allowing a free passage of bile very much as it would normally occur into the duodenum. Biliary secretion is markedly diminished during a period of fasting and especially when the fast is prolonged. The periodic flow of bile toward the duodenum shows diminution in both the frequency and the amount of discharge. When the animal is fed, biliary secretion is stimulated, and a marked increase in bile flow toward the duodenum results; this change is hardly noticeable during the first hour but becomes pronounced between the first and fourth hours after feeding. There follows a gradual slackening with a return to a rate of biliary flow like that observed early in the fasting period.

From the Author's Summary.

The Effect of Prolan A on the Adrenal Glands of Young Mature White Mice. F. S. Lopez, Frankfurt. Ztschr. f. Path. **46**:350, 1934.

Twenty-four test animals and thirteen controls were used for this experiment. In each group of experiments one litter was used. Most of the animals received subcutaneous injections of prolan A. Others were treated with prolan A and metacresol. At the conclusion of the experiment the adrenals were preserved in Bouin's solution and embedded in paraffin. Serial sections of the glands were made. Only the cortex of the adrenal gland revealed alterations. Three types of changes were encountered: *(a)* Marked hyperemia, most pronounced in the zona fasciculata and particularly at the border between this zone and the zona reticularis. *(b)* Hyperplasia. In all of the animals treated with prolan A the cortex was thicker than in the control animals. This was due to an increase of the cellular elements, particularly of those in the zona reticularis. Amitotic and mitotic cellular proliferations were present. *(c)* Degenerative changes. These were observed mainly in the zona reticularis. The cells contained many vacuoles, which sometimes fused by confluence.

Otto Saphir.

The Influence of a Blockade of the Reticuloendothelial System on Phagocytosis by Leukocytes. K. Rischke, Frankfurt. Ztschr. f. Path. **46**:557, 1934.

Rischke investigated the phagocytic power of the white blood cells within the peritoneal exudate produced in animals by intraperitoneal injection of physiologic solution of sodium chloride. Ground rice was employed as the object of phagocytosis. Almost uniform results were observed. Forty and thirty-three hundredths per cent of the polymorphonuclear leukocytes had phagocytosed the foreign material. One of the most constant observations following repeated experiments on the same animal was that this percentage of phagocytic cells remained almost the same. Two per cent of all the white blood cells observed were monocytes. Of these, 73.6

per cent were found to contain phagocytosed material. These represented the average figures. It was observed that when the cells of the reticulo-endothelial system had previously taken up large amounts of chinese ink, trypan blue, thorium dioxide (in colloidal solution), copper and gold, the phagocytic ability of the polymorphonuclear leukocytes and monocytes found in the exudate produced by intraperitoneal injection of physiologic solution of sodium chloride was markedly diminished. The results were independent of the type of substance used for blocking the cells of the reticulo-endothelial system. The phagocytic ability of the polymorphonuclear leukocytes when thus once lowered remained diminished for a prolonged period of time, and a reduced phagocytic power could still be demonstrated after two and one half years in one of the animals. The monocytes regained their phagocytic ability in a shorter time than the polymorphonuclear leukocytes. Nevertheless the percentage of phagocytic monocytes in the experimental animals remained less than that in the control animals after two and one half years had elapsed. The reason for the lowered phagocytic ability of these cells is not clear. Even if the hypothesis is accepted that the phagocytic action of white blood cells is similar to the action of the cells of the reticulo-endothelial system in storing foreign material, this still does not explain why injuries to the reticulo-endothelial system so radically alter the phagocytic power of the white blood cells. For the present, this observation must be accepted without an explanation. The fact is important, however, from the practical standpoint because it proves that any change in the reticulo-endothelial system affects the entire organism.

FROM THE AUTHOR'S SUMMARY.

Pathologic Anatomy

LIPOGRANULOMA OF THE BREAST. C. PANÀ, Frankfurt. Ztschr. f. Path. **46**:341, 1934.

An instance of fatty necrosis of the breast, a condition which Panà designates as lipogranuloma, was observed in a 71 year old woman. This lesion developed following a trauma. Histologically, many giant cells of the foreign body type were found in addition to an accumulation of eosinophil leukocytes, lymphocytes, endothelial cells with foamy cytoplasm and a few polymorphonuclear neutrophils. There was necrosis in the connective tissue, also much blood pigment. Microchemically, split products of fat could be demonstrated. The giant cells were explained as a reaction to a foreign body (the free fatty acids). While Panà does not believe that trauma is the principal cause of fatty necrosis, he considers it to be one of the final causes.

OTTO SAPHIR.

ANEURYSM-LIKE DILATATION OF THE FOSSA OVALIS EXTENDING INTO THE RIGHT AURICLE AND ATYPICAL ANEURYSM OF THE LEFT VENTRICLE. G. H. BARTSCH and A. POSSELT, Frankfurt. Ztschr. f. Path. **46**:358, 1934.

The rarity of aneurysm in the auricle as reported in the literature is stressed. Nineteen instances of auricular aneurysm were observed by these authors. They believe that such instances would be encountered with relative frequency if attention were focused on the foramen ovalis in routine examination. The aneurysm is interpreted as the result of differences in the pressure in the auricles. Anatomically, the pleomorphism of the fossa ovalis was noteworthy as regards size, shape and location. The increase of pressure in one auricle and the thinness of the fossa ovalis, on the other hand, were thought to form the basis for the development of the aneurysm. Often minute holes were found throughout the margins of the aneurysm. There is also one instance reported of an aneurysm of the posterior wall of the left ventricle which extended into the adjacent posterior portion of the interventricular septum. There was an associated severe sclerosis of the coronary arteries.

OTTO SAPHIR.

MEDULLA OF THE ADRENAL GLAND AND HYPERTENSION. W. FREI, Frankfurt. Ztschr. f. Path. **46**:523, 1934.

Frei demonstrates changes in the medulla of the adrenal gland in instances of hypertension. The belief is expressed that a correlation exists between the width and color of the medulla and hypertension. In this disease the medulla is wider than normal, the affinity to chromic stains is more pronounced, and more connective tissue is present. Because of these changes the color of the medulla is gray. In instances of infectious disease the medulla was smaller than normal.

OTTO SAPHIR.

Microbiology and Parasitology

THE SUBMAXILLARY GLAND VIRUSES OF RATS AND GUINEA PIGS. A. G. KUTTNER and T. T'UNG, J. Exper. Med. **62**:805, 1935.

It has not been possible to increase the virulence of the submaxillary gland viruses of guinea-pigs and rats by reducing the resistance of the animals through exposure to the roentgen rays or by the administration of testicular extract (Duran-Reynals factor) with the viruses. In guinea-pigs and wild rats with spontaneously infected submaxillary glands, the kidney has been found to contain the viruses in the absence of demonstrable pathologic changes. Direct injection of these viruses into the kidney produces only mild, circumscribed lesions. Following subcutaneous injection into white rats and guinea-pigs, the viruses are widely distributed two weeks after injection. They are present in the submaxillary glands, cervical lymph nodes, kidneys and lungs. They are not demonstrable at this time in the blood, liver or spleen. By the intratracheal injection of large doses of virus into guinea-pigs and rats, an interstitial bronchopneumonia can be produced, with thickening of the alveolar and bronchial walls and the presence of acidophilic inclusion bodies. No evidence was obtained to indicate that the multiplication of bacteria in the lung is greatly enhanced by the injection of these viruses.

FROM THE AUTHORS' CONCLUSIONS.

THE DISTRIBUTION OF SWINE INFLUENZA VIRUS IN SWINE. M. L. ORCUTT and R. E. SHOPE, J. Exper. Med. **62**:823, 1935.

The virus of swine influenza was found to be regularly present in the turbinates, tracheal exudate and lungs of infected swine but not in the spleens, livers, kidneys, mesenteric lymph nodes, colon mucosae, brains or blood. It was present in low concentration in the bronchial lymph nodes of two of eight animals. This localization of the virus in swine accords with its classification as a pneumotropic virus.

FROM THE AUTHORS' SUMMARY.

EXPERIMENTAL STUDIES ON ENCEPHALITIS. L. T. WEBSTER, G. L. FITE and A. D. CLOW, J. Exper. Med. **62**:827, 1935.

A test for measuring serologic properties protective against the virus of encephalitis (St. Louis type) is described. Normal noncontact serums and serums from persons supposed to have had no exposure to the disease do not protect against the virus. Of serums from tested convalescents from St. Louis encephalitis, 82.5 per cent show protective properties, as do at least 66 per cent of serums from tested persons thought to have had the disease. The protective activity of serums is maintained for at least two and a half years after the onset of the disease. In vitro aging of serum decreases its activity. Protection tests indicate that the virus was present as early as 1932 in Paris, Ill., that it spread through the north central states and reached New York in 1933, and that it was again active in the north central states in 1934.

FROM THE AUTHORS' CONCLUSIONS.

THE IMMIGRATION OF PNEUMOCOCCI III FROM THE BLOOD INTO THE THORACIC DUCT OF RABBITS. C. K. DRINKER and others, J. Exper. Med. **62**:849, 1935.

In rabbits given a large dose of virulent type III pneumococci by intravenous injection bacteremia develops, and within an hour the organisms may be cultivated from the lymph of the thoracic duct. The rapidity with which entrance into the lymph occurs appears to be correlated with the size of the dose injected. The organisms may become more numerous in the lymph than in the blood. If homologous or heterologous antiserums are injected, the blood may be sterilized, but, though the organisms may be lessened in number, sterilization of the lymph is not secured, at least within four hours, and in the intact animal living organisms must continue to enter the blood with lymph from the thoracic duct. In infected rabbits, after intravenous injection of considerable quantities of antiserum containing a moderate amount of agglutinin, no antibody appears in the lymph in the thoracic duct, although the presence of horse serum may be detected. The injection of a very large quantity of antiserum containing agglutinin in high titer is followed by the penetration of this antibody into the lymph. This, however, has failed to sterilize the lymph or to affect permanently the rate of multiplication of the pneumococci.

FROM THE AUTHORS' SUMMARY.

AN IMMUNOLOGIC STUDY OF THIRTEEN DIFFERENT STRAINS OF EQUINE ENCEPHALOMYELITIC VIRUS. B. F. HOWITT, J. Immunol. **29**:319, 1935.

Eleven strains of the virus of equine encephalomyelitis could be divided serologically into two distinct groups: a western and an eastern group (the latter the more virulent). A strain from Argentina behaved like the western group, while a strain from Russia differed from all others. Immune serums were obtained from guinea-pigs by repeated subcutaneous inoculations of active virus. Cross-neutralization tests in vitro and cross-protection tests in vivo were possible only among members of the same group. Some immunity was established, though not regularly, to viruses of the heterologous group by hyperimmunization. Young guinea-pigs born of immune parents were resistant to intracerebrally inoculated viruses of the homologous group, but they were less resistant to heterologous viruses than were the hyperimmunized older animals.

I. DAVIDSOHN.

THE NATURE OF BACTERIOPHAGE. J. D. LEMAR and J. T. MYERS, J. Infect. Dis. **57**:1 and 6, 1935.

1. *Extraction of Bacteriophage by Ether.*—Bacteriophage can apparently be extracted wholly or in part, unharmed, from aqueous solutions by ether. The rate and the completeness of extraction are influenced by agitation and by time. Unless there is a prolonged period of contact, some bacteriophage remains in the water phase. This residual bacteriophage may be restored to the original potency by serial transfer.

2. *Artificial Production of a Specific Lytic Agent Which Seems to Behave Like Bacteriophage.*—Incubation, autoclaving, secondary incubation and oxidation of bacterial broth cultures by hydrogen peroxide yielded lytic filtrates. Good results were obtained when such organisms as Bacillus coli, Bacillus typhosus, Salmonella enteritidis and Staphylococcus aureus were grown in broth for forty-eight hours, autoclaved twenty minutes at 15 pounds (6.8 Kg.) of pressure, again incubated for forty-eight hours at 37 C. and oxidized for forty-eight hours at 37 C. by 15 cc. of a 3 per cent dilution of hydrogen peroxide.

No lytic agent was produced when the period of secondary incubation was omitted unless the time of oxidation was prolonged for several days. Oxidation of living cultures yielded little or no lytic agent.

Filtrates made from cultures which had been autoclaved and permitted to incubate the second time without oxidation were not lytic.

Exposure for thirty minutes to a temperature of 75 C. completely destroyed the lytic agent. Repeated freezings with solid carbon dioxide and thawings did

not destroy it. The lytic agent could be removed from water by extraction with ether. It was filtrable and transmissible in series. It produced plaques on solid mediums. Very dilute or attenuated solutions caused stimulation of bacterial growth rather than lysis. FROM THE AUTHORS' SUMMARIES.

PRODUCTION OF AMORPHOUS EXTRA-BACTERIAL SUBSTANCES IN BACTERIAL CULTURES. L. DIENES, J. Infect. Dis. **57**:12 and 22, 1935.

1. *Oerskov's Milk Bacillus.*—The milk bacterium described by Oerskov was isolated, and it was confirmed that the extrabacterial substance produced abundantly by this bacterium on saccharose mediums consists of tiny nonstainable granules which are capable of multiplying without the intervention of bacteria. The granules under appropriate conditions grow in colonies free from bacteria. According to our observations, the colonies grow for one or two generations in transplants, and they grow abundantly from Berkefeld filtrates of young saccharose broth cultures plated immediately after filtration.

In contrast to Oerskov, we did not observe a growth-promoting effect of the bacteria on the granules. The presence of killed or living bacteria in the mediums and the proximity of bacterial colonies exerted no effect on the growth of granule colonies.

The extrabacterial substance takes its origin from disintegrated bacteria; but both the dextrose and the plain broth culture of the bacterium contain invisible elements which grow on saccharose agar plates into colonies of extrabacterial substance.

2. *Various Bacteria, Especially Gram-Positive Aerobic Spore-Bearing Bacilli.*—Bacteria of the subtilis group sometimes show phenomena closely related to those described in the preceding paper. On saccharose mediums they produce abundantly a nonstainable extrabacterial substance, capable of multiplication without intervention of bacteria. The extrabacterial substance spreads out from the subtilis colonies on the surface of nutrient agar plates, forming a halo around the colonies; and on mediums poor in nutrient material it forms tiny colonies inside the agar around the bacterium colonies.

The extrabacterial substance produced by subtilis strains could be transplanted for four generations on saccharose agar plates. The colonies on certain mediums present a definite morphologic structure and contain fairly large granules, faintly stained by crystal violet. So far, we have never succeeded in growing bacteria from these cultures, though sometimes bacterial forms are visible in them.

In subtilis cultures the derivation of the extrabacterial substance from the bacteria was not so clearly established as in the cultures of Oerskov's milk bacillus. The extrabacterial substance usually forms large capsules around the bacterium, and the capsular substance seemingly is capable of multiplying after separation from the bacterium. In physical and chemical characteristics, the extrabacterial substance is similar to the bacterial capsules. The halo formation and related phenomena are observed usually only for a short period after the isolation of the strains or after the cultivation from spores, during which time the bacteria grow in mucoid colonies. Every colony developed from a heated emulsion of spores reproduces the extrabacterial substance.

A gram-negative bacillus different from Oerskov's milk bacillus has been described as showing phenomena in every respect similar to those shown by Oerskov's bacillus. The origin of the granules in this strain was traceable to very large curved bacterial forms.

A continuous transition seems to exist from simple capsule formation to excessive production of capsular substances, and further to free multiplication of these substances in the mediums. The phenomena discussed in this paper probably represent the intensive development of a widely distributed property of bacterial growth.

The extrabacterial substance and the halo in certain stages of its development apparently consist of fine filaments; in preparations from fresh, extending halo, long fine filaments are visible.

The properties of the extrabacterial substance and the growth phenomena, especially the extension of the halo on the agar surface, strongly suggest that the extrabacterial substance contains living organisms. Morphologic observations give further support to this conclusion. FROM THE AUTHOR'S SUMMARIES.

THE PHASES OF TYPES OF H. PERTUSSIS. J. A. TOOMEY and others, J. Infect. Dis. **57**:49, 1935.

We were able to show by absorption and agglutination tests that Haemophilus pertussis is a species without any type variations. It has, however, different phases of existence as shown by absorption phenomena, but it would be difficult arbitrarily to limit these phases as Leslie and Gardner have done.

FROM THE AUTHORS' SUMMARY.

THE PRODUCTION OF ENTEROTOXIC SUBSTANCE BY BACTERIA. E. O. JORDAN and W. BURROWS, J. Infect. Dis. **57**:121, 1935.

Freshly isolated bacteria of various kinds (Staphylococcus, Streptococcus, Proteus, Bacterium coli, Bacterium aerogenes, Salmonella aertrycke) when grown under suitable conditions have been found capable of producing a substance that causes vomiting and other gastro-intestinal symptoms in monkeys. The use of a custard medium or the addition of starch to ordinary medium favors the production of the enterotoxic substance. By successive transfers on starch medium the property of producing enterotoxic substance was restored to a number of bacterial strains that had originally shown it but that had long given negative results. Although the procedures described do not invariably result in the production of toxic filtrates, it has always been possible to restore this property eventually to a given strain by intensive and repeated attempts.

Certain bacteria that had never yielded enterotoxic filtrates in previous laboratory tests gave positive results after they had been transferred on starch medium.

FROM THE AUTHORS' SUMMARY.

BENZIDINE BLOOD AGAR (PENFOLD) FOR ISOLATING STREPTOCOCCUS SCARLATINAE. R. TUNNICLIFF, J. Infect. Dis. **57**:147, 1935.

Benzidine blood agar plates (Penfold) are useful for the isolation of Streptococcus scarlatinae, which does not change the color of this medium, in contrast to some of its dissociants, which produce black or brown colonies.

For the identification of Str. scarlatinae, immunity tests need be made only with the streptococci from conical white colonies.

FROM THE AUTHOR'S CONCLUSIONS.

THE SURVIVAL OF TUBERCLE BACILLI SUBJECTED TO A VACUUM OF HIGH ORDER. T. S. POTTER, J. Infect. Dis. **57**:149, 1935.

Avian tubercle bacilli may retain viability when continuously confined for an extensive period under conditions such that the amount of molecular oxygen available is immeasurably small.

VARIATION IN CORYNEBACTERIUM DIPHTHERIAE. G. L. HOBBY, J. Infect. Dis. **57**:186, 1935.

In a certain strain of Corynebacterium diphtheriae, a spontaneous variation leading to a change from the rod to the coccoid form, and the reverse, have been observed.

Mucoid, smooth, rough and minute colonies of the rod form have been isolated. Mucoid and smooth colonies of the coccoid form have been isolated. A rough type consisting of filamentous, branching rods has been derived from the smooth

phase of the coccoid form. It has been shown that a transformation from the smooth phase of the coccoid form to the smooth phase of the rod form may occur through the intermediate stage of the rough phase derived from the coccoid form.

Single cell cultures of the coccoid form in the mucoid and smooth phases have been shown to be completely susceptible to the action of races of bacteriophage isolated (*a*) from the intestinal contents of persons with typical diphtheria, (*b*) from the intestinal contents and peritoneal washings of guinea-pigs infected with diphtheria bacilli and (*c*) from broth cultures that have stood at room temperature for from four to six weeks. Single cell cultures of the rod form in the mucoid, smooth and rough phases are completely resistant to the bacteriophage.

Eight races of bacteriophage isolated under anaerobic conditions from lysogenic variants of the smooth type of the rod form are active against the coccoid form in the mucoid and smooth phases but not against any other forms of this strain.

No correlation between virulence and toxigenicity has been observed. Evidence has been presented suggesting that the virulence of the rod form is increased by the presence of bacteriophage, which is active in vitro only against the coccoid form.

The ability of the coccoid form to produce toxin has been shown for the first time, thus indicating a fundamental relation between this and the characteristic rod form.

FROM THE AUTHOR'S CONCLUSIONS.

THE REVERSIBLE INACTIVATION OF BACTERIOPHAGE WITH SAFRANINE. A. P. KRUEGER and D. M. BALDWIN, J. Infect. Dis. **57**:207, 1935.

Safranine added to antistaphylococcus bacteriophage suspended in infusion broth of p_H 7.4 produces a heavy precipitate and inactivates the bacteriophage. The inactivation is in part photodynamic. By dissolving the precipitate in broth of p_H 6.5 about 25 per cent of the total bacteriophage inactivated can be reactivated. Adjustment of the supernatant fluid to p_H 6.5 yields an additional 10 per cent of the inactivated bacteriophage in an active form.

FROM THE AUTHORS' CONCLUSIONS.

THE PATHOGENICITY OF BRUCELLA ABORTUS FOR WHITE MICE. W. H. FELDMAN and C. OLSON JR., J. Infect. Dis. **57**:212, 1935.

Bovine and porcine strains of Brucella abortus, when injected intraperitoneally, are pathogenic for white mice. Agglutinins for Brucella are present in the blood of the inoculated animals, and the organism is recoverable from the spleen. Although grossly visible evidence of a diseased state infrequently occurs, rather characteristic lesions of the kidneys and liver and, less frequently, of the spleen, testes and epididymes may be observed microscopically. White mice should be satisfactory animals for the isolation of Brucella abortus from spontaneously infected material.

FROM THE AUTHORS' CONCLUSIONS.

CRYPTOCOCCI. R. W. BENHAM, J. Infect. Dis. **57**:255, 1935.

For the identification of cryptococci it is necessary to observe not only their morphologic character and colony form but their serologic and biologic reactions. Virulent strains can be recognized only by the results of their inoculation into animals.

Cryptococci parasitic on man may be divided into four groups on the basis of colony characteristics. These four groups are also sharply differentiated by agglutination tests.

In group 1 at least three species may be recognized: C. glabratus, C. ovoideus and C. aggregatus. They are not known to be pathogenic.

Strains in group 2 probably form one species described as C. mucorugosus. It is not known to be pathogenic.

Strains in group 3 probably form one species—C. hominis, but this includes virulent strains causing fatal infection in man and animals and avirulent strains

found as harmless parasites on normal persons. Two varieties may be recognized on the basis of virulence or of antigenic and slight morphologic differences from the type strains.

Strains in group 4 belong probably to several species none of which has been accurately defined. All are characterized by the formation of pink or red pigment. None is known to be pathogenic. FROM THE AUTHOR'S SUMMARY.

THE DISSOCIATION OF CLOSTRIDIUM WELCHII. F. A. STEVENS, J. Infect. Dis. **57**: 275, 1935.

Three stable variants have been obtained from several strains of Clostridium Welchii. These variants seem comparable with the encapsulated mucoid, the non-encapsulated smooth and the rough variants of Pneumococcus described by Dawson. An additional colony called the omega variant has been observed. When these four variants are compared in the M, S, R, omega order, a gradual increase in the average length of the bacillus is observed, together with a tendency toward imperfect, delayed and incomplete fission. In the omega colony the clean sharp fission observed in mucoid variants is replaced by a disintegration of parts of the long filaments characteristic of these colonies.

Two types of unstable hybrid variants have been isolated. In one type different parts of a colony have the gross and microscopic characteristics of the pure variants. In the other type the microscopic characteristics of the cells are temporarily confused so that capsules characteristic of mucoid bacilli may even occur on rough bacilli to which they are usually foreign.

It appears that each individual quality of a variant is transmitted hereditarily through either the cell or its spore, and that certain qualities are grouped together to form complexes recognized as the stable variants.

FROM THE AUTHOR'S SUMMARY.

A MALARIAL PARASITE INFECTING ALL BLOOD AND BLOOD-FORMING CELLS OF BIRDS. C. G. HUFF and W. BLOOM, J. Infect. Dis. **57**:315, 1935.

Plasmodium elongatum has a daily cycle with the peak of segmentation occurring between 8 and 10 a. m.

In contrast to other malaria parasites, this parasite is capable of living in all blood and blood-forming cells of the canary, including granular leukocytes. Although all of the asexual stages are found in all of the blood and blood-forming cells, the vast majority occur in cells of the erythrocyte series; the gametocytes are found only in normoblasts and erythrocytes.

Only the parasites in cells with obvious hemoglobin produce pigment.

The elongate merozoites of this plasmodium resemble those of the coccidia.

The systematic position of this plasmodium and its relations to the cells it inhabits are discussed. Some of the relations among the blood-forming cells in these canaries are commented on. FROM THE AUTHORS' SUMMARY.

HISTOLOGIC REACTION TO THE VIRUS OF ROCKY MOUNTAIN SPOTTED FEVER IN CHICK EMBRYOS. R. D. LILLIE, Pub. Health Rep. **50**:1498, 1935.

The focal lesions of Rocky Mountain spotted fever in chick embryos were as follows: (1) perivascular or interstitial infiltration by lymphocytes, occurring in the fetal membranes, skin, muscles, kidneys, wolffian bodies, heart, liver, serosae of the gastro-intestinal tract, gizzard muscle, meninges and choroid plexi; (2) focal adventitial fibroblast proliferation of blood vessels, vascular endothelial swelling and occasional vascular thrombonecroses, occurring only in the fetal membranes. Other changes were exaggeration of normal myeloid collections in the lungs and proventricular mucosa, occurrence of these in the pancreas and a tendency to replacement of granular myelocytes in these collections and in the splenic pulp and bone marrow by nongranular promyeloid and lymphoid cells.

FROM THE AUTHOR'S SUMMARY.

EFFECT OF RADIUM EMANATIONS ON BACTERIA. R. R. SPENCER, Pub. Health Rep. **50**:1642, 1935.

Our results seem at first to suggest that bacteria are more insensitive to radium emanations than higher forms, in which there has been found a definite correlation between frequency of mutation and intensity and time of irradiation. However, bacteria have apparently no morphologically definite chromosomes, and the nucleus is assumed to be in the disperse form. In the absence of chromosomes there is no reason to assume any definite fixed order of the genic units such as occurs in the chromosomes of higher forms. These structural differences between bacterial cells and the cells of higher forms may account, in part, for the apparent random distribution of mutations which was actually observed. Furthermore, bacteria have no mechanism comparable to mitosis, which serves to insure both quantitative and qualitative equal distribution of the nuclear material to the daughter cells.

Three facts should be emphasized: (*a*) The mutations observed in this research are not necessarily criteria of the actual mutations which occur either as to number or as to the ratio in which these mutations occur. (*b*) In a bacterial cell with a disperse nucleus and no sexual reproduction it is impossible to be certain as to whether a given "mutation" is such in the sense ordinarily used, since it may be a cytoplasmic and not a nuclear change. That cytoplasmic changes may be heritable until sexual reproduction intervenes has been shown by Jollos (1914). (*c*) In the higher organisms, e. g., Drosophila, by far the greater number of mutations are lethal. They may be demonstrated through breeding, but such a demonstration is probably impracticable if not impossible with bacteria.

At the present stage of our work we refrain from drawing definite conclusions or making generalizations. Much more work is needed. The data, however, have encouraged us to attempt to employ a similar technic in the study of various organisms higher than bacteria in the biologic scale which possess different types of nuclear structure in order to ascertain whether the type of result is, in fact, correlated with the nuclear morphology as here suggested.

FROM THE AUTHOR'S DISCUSSION.

THE PARACOLON GROUP OF BACTERIA. B. R. SANDIFORD, J. Path. & Bact. **41**:77, 1935.

The term "paracolon" is fittingly applied to the group of coliform organisms which culturally resemble Bacillus coli except that they either do not ferment lactose or ferment it atypically. The members of the group do not agglutinate with paratyphoid agglutinating serum, and the group as a whole is serologically heterogenous while showing some small degree of common antigen between individual strains. In actual practice, their positive indole reaction readily distinguishes the paracolon from the paratyphoid group. Their common lack of motility is a further distinguishing feature. The presence of paracolon bacilli in a stool is most probably without etiologic significance. As with other intestinal coliform organisms, the paracolon bacilli are potential pathogens in the body outside the intestinal tract. The organism known as Bacterium asiaticum (Castellani) is better regarded as a member of the paracolon group than as a specific pathogenic organism. The fermentation of rhamnose shows a mechanism different from that commonly found in the fermentation of sugars by bacteria.

FROM THE AUTHOR'S CONCLUSIONS.

ONE HUNDRED AND SIXTY-SIX CASES OF DIPHTHERIA CORRELATED WITH THE TYPES OF BACILLUS DIPHTHERIAE CONCERNED. J. F. MURRAY, J. Path. & Bact. **41**:97, 1935.

One hundred and sixty-six strains of Bacillus diphtheriae were examined as regards their appearance on McLeod's medium, their morphology and their fermentative reactions. It was found possible to classify them into the three types described by McLeod. There were, however, two subgroups in the gravis type,

also in the "intermediate" type. It was found that each type had a predominant morphology associated with it. The gravis type was not found to be associated with a severe type of clinical case. The clinical cases associated with the "intermediate" type were of greater severity than those associated with the mitis type.

FROM THE AUTHOR'S SUMMARY.

THE PRODUCTION OF PNEUMONIA IN MICE BY BACTERIA AND FILTERABLE VIRUSES. L. HOYLE, J. Path. & Bact. **41**:163, 1935.

Aspiration pneumonia can be produced in mice by intranasal inoculation, under ether, of various pathogenic bacteria, namely, Haemophilus influenzae, Pneumococcus, Friedländer's bacillus, Staphylococcus aureus, Proteus vulgaris and a gram-negative coccobacillus of mouse origin. Pneumonic lesions can be produced in mice in a similar manner by the virus of swine influenza and by the B. W. and W. S. viruses isolated from human influenza by Andrewes, Smith and Laidlaw (*Lancet* **2**:859, 1934). These lesions have the same characters as the aspiration pneumonias producible by pathogenic bacteria and cannot be considered to represent a specific illness comparable to human epidemic influenza. An apparently non-bacterial agent similar to the B. W. and W. S. viruses has been isolated from a case of acute coryza.

FROM THE AUTHOR'S CONCLUSIONS.

Tumors

FASCIAL SARCOMA AND INTERMUSCULAR MYXOLIPOSARCOMA. J. EWING, Arch. Surg. **31**:57, 1935.

The term "fascial sarcoma" should be restricted to the fibroma, fibrosarcoma, fibrochondroma or parosteal osteosarcoma originally described and designated as fascial sarcoma by Virchow. It should not be employed for intermuscular myxosarcoma. The intermuscular myxosarcoma, often called fascial sarcoma, is probably derived from fat lobules and presents the structure of embryonal mucous tissue or embryonal fat tissue. It is rarely, if ever, of traumatic origin and is often radiosensitive. The common liposarcoma of the trunk and limbs is derived from adult fat tissue and presents the structure of large granular cells such as those seen in chronic inflammation of fat tissue. The structure varies greatly with the degree of malignancy. It seems to be occasionally of traumatic origin. The degree of radiosensitivity of the primary tumor is uncertain, but the recurrent tumors are radioresistant. It appears that two types of liposarcoma may be recognized, one the myxoliposarcoma of embryonal structure and the other the granular cell liposarcoma of the adult type. Liposarcoma of both types is comparatively common in the region of the hip, knee, shoulder and trunk. It runs a characteristic clinical course, usually recurring after operation and proving fatal from infection, sepsis and metastases to the lungs. Since some are radiosensitive, it is recommended that all bulky tumors of the soft parts be submitted to treatment with high voltage radiation before resort to surgical intervention.

FROM THE AUTHOR'S SUMMARY.

ADENOMA OF ADRENAL CORTEX SIMULATING PITUITARY BASOPHILISM (CUSHING'S SYNDROME). R. M. CALDER and F. W. PORRO, Bull. Johns Hopkins Hosp. **57**:99, 1935.

A case is reported which was characterized by rapidly acquired, plethoric obesity, hypertrichosis, amenorrhea, hypertrophy of the clitoris, generalized osteoporosis, vascular hypertension and moderate polycythemia. This case was thought clinically to be an instance of pituitary basophilism (Cushing's syndrome), but at autopsy a large primary adrenal neoplasm was found, and the hypophysis was normal. The questions of differential diagnosis and treatment are discussed.

FROM THE AUTHORS' SUMMARY.

TAR CANCER OF THE LIP IN FISHERMEN. P. SHAMBAUGH, J. A. M. A. **104**:2326, 1935.

Fishermen in the region of Massachusetts are exposed, in the handling and repairing of tarred nets, to the most strongly carcinogenic type of tar, namely, the tar produced in horizontal retort gas-works. The lips are especially apt to be contaminated with the tar owing to the frequent practice of holding the tar-smeared needle in the mouth while repairing the nets. In the eight cases of cancer of the lip in fishermen here reported it is believed that such exposure to tar was an important factor. These observations suggest that exposure to tar may be partially responsible for the apparent high incidence of cancer of the lip in fishermen.

FROM THE AUTHOR'S SUMMARY.

RELATION OF LEUKEMIA OF ANIMALS TO LEUKEMIA OF MAN. J. FURTH, H. W. FERRIS and P. REZNIKOFF, J. A. M. A. **105**:1824, 1935.

Leukemia of man is essentially the same disease as leukemia of mice. Both the acute and the chronic forms, lymphoid as well as myeloid, are neoplastic diseases. The immature blood cells in leukemia are malignant cells, which may form tumors or diffuse infiltrations and possess characteristics of their own. Studies of leukemia of the mouse indicate that the disease, like cancer, is of multiple etiology; its development and manifestations are dependent on intrinsic (genetic) and extrinsic factors. An analysis of these factors in the mouse and their rôle in the human disease require further study. FROM THE AUTHORS' CONCLUSIONS.

VITAL STAINING and WET FILMS IN THE DIAGNOSIS OF LESIONS OF THE CERVIX. R. K. BOWES and N. R. BARRETT, Surg., Gynec. & Obst. **60**:1072, 1935.

In the hands of the authors, staining by aqueous solution of iodine proved inconstant, difficult to interpret and influenced by factors apart from pathologic lesions, such as age and phases of the menstrual cycle. Cervical cancer is rarely seen in the preulcerative stage, and normal iodine staining of the cervix does not exclude carcinoma low down in the cervical canal. The conclusion reached is that visual and manual examination, supplemented in doubtful cases by microscopic study of a wet film of material removed for biopsy, is the most satisfactory means of arriving at a correct diagnosis of lesions of the cervix. Biopsy material, obtained by means of a special punch, can be teased out on a slide and stained within a few minutes.

WARREN C. HUNTER.

THE EFFECTS OF METHYLENE BLUE AND OTHER OXIDATION-REDUCTION INDICATORS ON EXPERIMENTAL TUMORS. M. M. BROOKS, Univ. California Publ., Zool. **39**:293, 1934.

Of five oxidation-reduction dyes which were injected into transplantable tumors in rats and mice, methylthionine chloride, U. S. P. (methylene blue), was the only one which was efficient in causing regressions. Methylthionine chloride gave 44 per cent regressions in rats as compared with 8 per cent in the controls (including both the untreated ones and those receiving Ringer's solution) and 25 per cent in mice as compared with 3 per cent in the controls.

FROM THE AUTHOR'S SUMMARY.

THE PRODUCTION OF TUMOURS IN THE FOWL WITH 1:2:5:6-DIBENZANTHRACENE. I. BERENBLUM and L. P. KENDAL, Brit. J. Exper. Path. **15**:366, 1934.

Repeated injections of a 0.007 per cent colloidal solution of dibenzanthracene in water into the breast muscle led to the production of spindle-cell sarcoma in eight of twelve birds which survived more than twelve weeks. The total amount of dibenzanthracene injected was about 1.8 mg. Secondary deposits were found in three birds. Five of these tumors were transplanted into other birds, and two

grew successfully. In one of the inoculated birds metastases were present in the lungs. The administration of kieselguhr together with colloidal dibenzanthracene did not appear to influence significantly the development of tumors. Eighteen months after intramuscular injections of 0.6 mg. of dibenzanthracene none of the substance could be detected in the muscle about the site of injection.

FROM THE AUTHORS' SUMMARY.

ESTIMATION OF THE SIZE OF A FOWL TUMOUR VIRUS BY FILTRATION THROUGH GRADED MEMBRANES. W. J. ELFORD and C. H. ANDREWES, Brit. J. Exper. Path. **16**:61, 1935.

Partially purified virus of Rous fowl tumor was filtered through graded collodion membranes. The least permeable membrane permitting virus to pass had an average pore diameter of 0.25 micron, the indicated end-point for complete retention being 0.2 micron. Reasons are given for believing that this indicates that the particles of virus have a diameter of about 0.1 micron. If so, the Rous virus resembles in size the larger rather than the smaller viruses and should be just within the limits of resolution by ultraviolet rays. A few experiments suggest that the Fujinami virus has about the same size as that of the Rous 1, whether the tumors from which it is obtained grow in fowls or ducks.

FROM THE AUTHORS' SUMMARY.

EFFECT OF INTERFERENCE WITH THE VASCULAR SUPPLY ON THE INDUCTION OF DIBENZANTHRACENE TUMORS. J. W. ORR, Brit. J. Exper. Path. **16**:121, 1935.

Fibrosis of the subcutaneous tissue produced by insertion and subsequent removal of linen threads resulted in an acceleration of the induction of tumor in mice by means of 1:2:5:6-dibenzanthracene. Weekly injections of epinephrine hydrochloride (British Pharmacopœia) under the treated epithelium led to a more rapid appearance of dibenzanthracene tumors. The effect appears to be due to the epinephrine and not to any other constituent of the solution. Ephedrine sulfate had no effect on the rate of induction of tumors by dibenzanthracene.

FROM THE AUTHOR'S SUMMARY.

MALIGNANT HEMANGIO-ENDOTHELIOMA. E. DE BARY, Frankfurt. Ztschr. f. Path. and C. H. ANDREWES, Brit. J. Exper. Path. **16**:271, 1935.

We finally succeeded in adapting the "inflammatory" strain of virus to growth in cultures of rabbit testis by regularly selecting from a number the one flask in which the virus had grown best and using that to inoculate further cultures. After assisting the initial adaptation in this way, we were soon able to cultivate the virus without difficulty and passed it through ten cultures in series. We were unable to grow this culture-adapted virus in rabbit fibroblasts but are reluctant to conclude from this failure that the virus cannot infect these cells in the living animals.

FROM THE AUTHORS' SUMMARY.

MALIGNANT HEMANGIO-ENDOTHELIOMA. E. DE BARY, Frankfurt. Ztschr. f. Path. **46**:410, 1934.

A tumor the size of a cherry was removed from a 24 year old woman. It revealed much fibrosis with hyalinization and small cysts. There was also a new formation of blood vessels with hemorrhage and necrosis and many large irregular tumor cells. The diagnosis was hemangio-endothelioma. A few months later the tumor recurred. There were large round and oval cells with many mitotic figures and much necrosis in the specimen. The diagnosis was diffusely infiltrating cellular, hemangio-endothelioma, a malignant tumor. The patient was given roentgen treatments. Several months later the tumor recurred in the form of many minute and larger dark blue nodules. Similar nodules developed later on the scalp, neck

and back. The patient died about one year after she had noted the first tumor. There was no autopsy. In the second instance a tumor was found in the left side of the nasopharynx and left tonsil in a 43 year old man. He was submitted to roentgen treatment. A biopsy specimen was not obtained at that time. The tumor disappeared, but four months later the patient was readmitted with a diagnosis of mediastinal tumor. The autopsy revealed a mediastinal tumor the size of a fist, which microscopically proved to be a diffusely infiltrating hemangio-endothelioma. The nasopharynx and left tonsil showed no tumor. De Bary believes that the manifold appearance of the hemangio-endothelioma is an example of true metastases.

OTTO SAPHIR.

TWO CASES OF ARRHENOBLASTOMA OF THE OVARY. E. BENECKE, Virchows Arch. f. path. Anat. **294**:38, 1934.

This contribution from R. Meyer's institute opens with a brief discussion of the disgerminoma of the ovary, which according to Meyer has no hormonal action, and of the granulosa cell tumor, which produces the female hormone. Then follows a fuller discussion of the masculinizing tumors of the ovary. These fall into two classes: (1) the "large cell" tumors, which are composed of adrenal cortical tissue or perhaps of lutein cell derivatives, and (2) the arrhenoblastoma, which produces male hormone. Tumors of the latter group are divided into two main types: the tubular, composed of epithelial tubules like those of the rete testis, and the solid cellular variety made up of indifferent blastoma. Intermediate forms may be cellular or sarcoma-like, with glandular or tubular areas. The hormonal activity appears to vary inversely with the degree of differentiation. Benecke abstracts reports of six cases of arrhenoblastoma from the recent literature and describes in great detail two cases of his own. In his own cases the tumor was histologically of the intermediate type.

O. T. SCHULTZ.

CEREBRAL GLIOMA IN A HEN. V. BELMONTE, Virchows Arch. f. path. Anat. **294**: 328, 1935.

Notice of this brief article is included for those interested in the tumors of domestic animals. According to Belmonte, glioma of the brain in birds has not previously been recorded. He describes an astrocytoma in a hen.

O. T. SCHULTZ.

THREE CASES OF PARATHYROID TUMOR. E. RUTISHAUSER, Virchows Arch. f. path. Anat. **294**:570, 1935.

Three cases of parathyroid tumor are reported. In two the tumor was associated with slight or latent osteitis fibrosa and in one, with a more marked degree of this condition. One tumor was a carcinoma; the others, adenomas. Owing to the difficulty at times of differentiating histologically between thyroid and parathyroid adenoma, functional studies are important. Especially stressed is the rapidity with which injections of the suspected material may overcome the osseous changes following experimental parathyroidectomy.

O. T. SCHULTZ.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 23, 1936

WILLIAM C. VON GLAHN, *President*

IRVING GRAEF, *Secretary*

NATURE OF THE ROSENTHAL FIBERS IN CASES OF SYRINGOMYELIA WITH INTRAMEDULLARY TUMOR. AMOUR F. LIBER (by invitation).

The lesion which bears Rosenthal's name was first described by him in 1898 in association with gliotic syringomyelia with intramedullary tumor of the spinal cord. A second case was reported in 1920 by Bielschowsky and Unger, who named the lesion "Rosenthal fibers." Since then three other cases of Rosenthal fibers have been reported, making a total of five reported cases. In all the cases there was syringomyelia with intramedullary tumor of the cord or of the medulla.

Rosenthal fibers are found outside the tumor, in the gliosis about syringomyelic cavities and in solid gliotic masses. They are microscopic and are shaped like very elongated cones, with one end broader and the other long, tapering and pointed. Their outstanding tinctorial affinity is an intense brownish-black or coal-black color with hematoxylin lakes, particularly with iron alum hematoxylin. They are oriented in a general way like the glia fibers among which they occur.

Four interpretations have been placed on the nature of Rosenthal fibers, as follows: 1. They are glia fibers containing a substance peculiarly avid toward hematoxylin (Rosenthal). 2. They are a pathologic new growth of myelin (Benda). 3. They are cytoplasmic processes of glia cells which have retained their embryonal myelin-building function (Bielschowsky and Unger). 4. They are fragments of degenerated and calcified nerve fibers (Tannenberg).

The case reported here is that of a man aged 48 who died at the New York City Hospital after thirty-four months of illness consisting chiefly of progressive spastic tetraplegia. Autopsy showed an ependymoma of the infra-olivary portion of the medulla and of the first two cervical segments of the spinal cord. Above and below the tumor were gliotic stalks and syringomyelic cavities. Rosenthal fibers were found at several levels in the gliotic area. They were often extremely abundant. Their morphology, relations and staining qualities corresponded to the original description by Rosenthal. In addition, it was noted that the Rosenthal fibers were visible unstained because of their peculiar refringence. Their visibility was greatest in a medium with a relatively low index of refraction, such as water or glycerin jelly. They shared this optic quality and most of their staining affinities with only one other element, the red blood cell.

From a study of the spatial relations of Rosenthal fibers to other elements, it was concluded that the former could not be identified with glia fibers, glia cytoplasm, myelin or nerve fibers. Thus none of the four hypotheses mentioned could be corroborated in the present case.

Infiltrating cells and particularly siderin-holding macrophages, which were very abundant in some of the regions of gliosis, were sparse where Rosenthal fibers occurred.

Microchemical tests for lipids, amyloid, fibrin, mucin, ferric ions, ferrous ions and calcium were all negative. The many similarities between the staining qualities of the Rosenthal fibers and those of the red blood cells suggested that the fibers might contain a hemoglobin-like substance. This hypothesis was tested by employ-

ing two methods of elective staining for hemoglobin—Miller's hematoxylin method (*Frankfurt. Ztschr. f. Path.* **11**:403, 1911) and Brown's peroxide acid ferrocyanide method (*J. Exper. Med.* **13**:447, 1911). The latter, which proved to be the more elective, stains hemoglobin and its immediate iron-containing heme derivatives a special shade of blue. The Rosenthal fibers gave the characteristic reaction with both methods. The intensity of the blue in the Rosenthal fibers stained by Brown's method was very similar to that in the red blood cells. This fact, together with the close similarity of the indexes of refraction of these two elements, suggests that the heme substance in the Rosenthal fibers was not mixed with other material to any appreciable extent.

It is suggested that the term "Rosenthal fibers" be replaced by heme bodies.

This paper will appear in full in the *Journal of Nervous and Mental Disease.*

DISCUSSION

PAUL KLEMPERER: I should like to ask Dr. Liber if he can explain why the hemoglobin body should be so unusual, occurring in this one condition only. Why not in other conditions in which there is hemorrhage? I have never seen anything like it in other organs. The nearest like it, I think, are the faintly staining bodies which one finds in the sinuses of the spleen in hemolytic anemia.

DR. AMOUR F. LIBER: This question has indeed occurred to me. I do not know what the explanation is. On seeing the slides in this case I said that I had never seen anything like it, nor had Dr. Lisa. Several other persons whom I asked about this also said that they had never seen anything like it. In the literature I have not been able to find any representation of an object closely resembling this except in reports of syringomyelia, and not in all reports of syringomyelia but only in those in which a tumor of the cord is described. Why it should be so is obviously difficult to explain. There is a vast literature on syringomyelia, enormous numbers of cases having been reported, and I think Dr. Klemperer's question properly includes the following question: Why is this body so rare even in syringomyelia and even in syringomyelia with intramedullary tumor? That can perhaps be answered conditionally. There is reason to think that it may not be so rare as the literature indicates: A suggestive case of syringomyelia associated with tumor was reported by Leupold in 1919. He did not describe Rosenthal fibers but mentioned fragments of myelin. The same case was taken up again by Kirch nine years later and described at length. He did not agree with Leupold in all of the latter's interpretations. For instance, Kirch described these fragments of myelin as Rosenthal fibers. It may be that such fibers have to some extent passed unnoticed, perhaps because neuropathologists have the habit of interpreting the nature of objects more by the elective stain than by a whole group of circumstances which would probably define them better. In this case these objects stain somewhat like myelin; that is, they take the same stain, but that is as far as the resemblance goes.

As to why they are not seen in other conditions, free hemoglobin is undoubtedly seen in other conditions, and Dr. Klemperer mentioned one of them. It is seen in the kidney in other hemolytic disturbances which are produced experimentally and observed clinically, such as potassium chlorate poisoning. The fact that hemoglobin stains faintly is not noteworthy, because with ordinary stains Rosenthal fibers stain very faintly, whereas with a stain such as iron hematoxylin, which is not used currently, both stain intensely. In other words, it is perhaps fortunate that the Rosenthal fibers were observed by one who happened to use the neuropathologic technic which stains hemoglobin intensely.

ATYPICAL AMYLOIDOSIS WITH INVOLVEMENT OF THE LUNGS. HENRY W. FERRIS.

Amyloid in the lungs has been described infrequently, though it was first noted by Virchow in 1857. It occurs in the form of localized nodules or masses unassociated with amyloid elsewhere or, more frequently, diffusely distributed in the lungs in association with generalized amyloidosis. In many instances there is scant involvement of the walls of pulmonary blood vessels and alveoli, while in other

cases the architecture of the lung is greatly distorted by the large amount of amyloid, frequently in nodules. The reactions with the special stains for amyloid are often atypical. In most cases there is no preceding or concurrent chronic disease which has an etiologic relationship.

Two cases of amyloidosis of the lungs are reported: The first case occurred in a white man 78 years old who had an extensive carcinoma of the bladder with bilateral hydro-ureter, hydronephrosis and pyelonephritis. In the lower lobe of the right lung was a firm area which measured about 5 by 3.5 by 2.5 cm. It contained dilated bronchioles filled with pus. These were surrounded by dense pale gray tissue. Microscopically much of this tissue was amyloid in the walls of arteries and alveoli. There was considerable amyloid in the spleen but not in other organs.

The second case reported was that of a white man 52 years old who died with signs and symptoms of congestive heart failure. There was moderate peritoneal and pleural effusion. The lungs together weighed 1,710 Gm. They contained many glistening gray nodules, tapioca-like, the largest of which were about 0.4 cm. in diameter. These were more numerous in the lower lobes. Microscopically many of the alveolar lumens were narrowed by the widening of the septums due to the extensive deposition of amyloid. Blood vessels and bronchi in the lungs were also involved. In the heart, spleen and lymph nodes amyoid was abundant, while in the liver, kidneys and several others organs it was scant.

The conclusion is drawn that advanced amyloidosis of the lungs and heart unassociated with any of the usual etiologic diseases may produce cardiac failure and death.

DISCUSSION

JOSEPH C. ROPER (by invitation): From a clinical point of view the chief conviction in this case was that neither I nor my associates knew what was the matter with the patient. On admission of the patient to the New York City Hospital the absence of any peripheral or retinal evidence of arteriosclerosis and the absence of hypertension and of valvular lesions or other clinical observations that offered explanation for the obvious circulatory failure convinced us that the underlying condition was unusual. Although the history did not support it, a tentative diagnosis of obliteration of the pericardium was made with the feeling that this would explain the enlargement of the heart and liver and the congestion of the lungs. Atypical amyloidosis was never considered even subconsciously. It is a matter of regret that at present clinical knowledge does not permit one to identify this condition clinically. With such a pronounced pathologic condition there must be some clinical chemical changes that laboratory men will in the future be able to detect.

DAVID PERLA: I was much interested in these cases because I have seen several cases of so-called primary amyloid disease, and in one of these I observed a similar marked involvement of the myocardium; the patient's heart was very large, and his death was due to heart failure. Just why the disease should lead to such marked cardiac hypertrophy I do not know. In any case of extensive destruction of the myocardium as a result of coronary thrombosis, unless there is antecedent hypertension or some other factor which predisposes to hypertrophy, no gross cardiac hypertrophy results. Why pressure destruction in amyloidosis leads to such profound hypertrophy of the heart is difficult to understand, unless the enlargement is due to the actual bulk of the amyloid material deposited.

I should like to ask whether in Dr. Ferris' first case the lumens of the blood vessels of the lung were sufficiently small to cause increased tension in the pulmonary circulation, and whether there was believed to be a mechanical interference with the blood flow, or was the amyloid distributed sufficiently widely to produce diffuse pulmonary fibrosis?

I have seen two instances of giant cell formation in association with amyloidosis, both in the spleen. There have been a number of instances reported, but it is of interest that this association is rare. In a series of 120 or 130 cases of diffuse amyloid disease I encountered giant cell formation only twice. One can see giant

cell formation in deposits of amyloid following experimental injection of sodium caseinate, and one can see the amyloid deposits surrounded by giant cells which show evidence of phagocytosis.

Several instances have been reported in which there was some obscure etiologic factor, such as myeloma. Jacobson reported two cases in which deposits of amyloid were associated with plasma cell myelomas, which were so small that they gave no gross manifestation during life, but microscopic examination of the vertebrae revealed them.

HENRY W. FERRIS: In reply to Dr. Perla's question about the hypertrophy of the heart, I think the size of the heart was due in large part to the deposition of amyloid. There was obvious hypertrophy shown by microscopic section. I think the hypertrophy was partly compensation for the atrophy of some of the muscle fibers. It is difficult to say how much of the increased size of the heart was due to hypertrophy and how much to amyloid deposits.

As for the rôle of a decrease in the size of the vessels of the lungs in producing hypertrophy, I think that might have played some part. The lung was obviously consolidated with the amyloid.

In regard to the giant cells I cannot say very much except that they were found in both these cases. I had never seen giant cells in amyloid before. In the first case there was no amyloid in the heart; it was present in the heart in the second case. In the latter the amyloid was scattered throughout both lungs but was more obvious in the lower lobes.

There was no myeloma present in these cases grossly; there may have been a microscopic myeloma.

TWO INSTANCES OF SPECKLED SPLEEN (FLECKMILZ) OF FEITIS. H. BRODY and A. Z. KALISCH (by invitation).

Two cases of speckled spleen which agree in most details with the original cases of Feitis were described. In each instance the disease was associated with vascular lesions of the nature of proliferative thrombosis, generalized in one case and in both cases associated also with mild vascular disease of the kidney. A third case was described in which the typical speckled appearance was shown grossly and multiple necroses and infarcts microscopically, unassociated with any vascular changes, which undoubtedly represented the purely toxic type of the lesion.

DISCUSSION

PAUL KLEMPERER: This paper is interesting, and it would take much time to discuss all the points touched on. I should like to say a few words in regard to speckled spleen in general. I do not think one should be surprised to find it in instances of severe vascular lesions, particularly in cases of malignant nephrosclerosis with necrotizing arterial changes in the kidney. Much more interesting are the cases of speckled spleen in which no vascular lesions are present, or in which there is only thrombus formation in the vessels without striking alteration of the wall. In such cases the condition was considered as toxic speckled spleen. Such multiple necroses in the spleen without any vascular lesion have been seen by me two or three times in cases of acute lupus erythematosus, and in the same cases multiple necroses were present in the lymph nodes.

I was glad that Dr. Brody did not limit his remarks to the spleen. It is not the spleen alone which is involved, but the spleen is the most strikingly involved. The more routine histologic studies one makes, the more one finds small necroses in many organs, particularly in the adrenal glands. Vascular lesions will produce the same multiple necroses in other organs, for instance, in the pancreas. Hyaline thrombi may also cause smaller or larger necroses. One finds them quite frequently in routine examination of the organs in cases of severe infections. One is quite surprised how striking such lesions are microscopically, while macroscopically hardly anything can be seen. This is particularly true in the adrenal glands and kidneys. In one case thrombi were responsible for multiple ulcers of the large

intestine. In such cases one finds capillaries and arterioles filled with thrombi, which one is inclined to call hyaline thrombi. By shutting down the light, however, one can see that they are granular, and I think they are platelet thrombi.

I want to mention four cases which I have seen of a condition that must be designated as multiple systemic thrombosis in which practically every organ contained an enormous number of thrombi, which I regarded as platelet thrombi exclusively within arterioles and arterial capillaries. In one of these cases, there was a speckled spleen due to the presence of multiple thrombi.

In regard to the proliferations of endothelium which Dr. Brody has shown, I wonder if these are not organizing parietal thrombi.

IRVING GRAEF: In regard to the cases in which multiple necroses of the spleen and other organs are not associated with vascular lesions, I should like to call attention to a case studied at Bellevue Hospital and reported by Sabin and Wright in the *Journal of Experimental Medicine* (**59**:115, 1934) in which a new virus was reported, the B virus. It had infected a bacteriologist via a monkey bite and caused his death. Multiple necroses were found in the regional lymph nodes and spleen, with widespread necrosis of the adrenal glands, and no vascular lesions were found.

ISADORE E. GERBER: In connection with what Dr. Graef has pointed out, Roehrer in 1932, in a pathologic study of hog cholera and of hogs immunized with the specific virus, obtained changes in the spleen characteristic of speckled spleen and, in addition, necrosis of the renal cortex.

CHICAGO PATHOLOGICAL SOCIETY

PERCIVAL BAILEY, *President, in the Chair*

Regular Monthly Meeting, March 9, 1936

EDWIN F. HIRSCH, *Secretary*

THE HERPETIC ANTIVIRAL PROPERTY OF THE BLOOD IN RELATION TO SEX, PREGNANCY AND MENSTRUATION. N. PAUL HUDSON and ENID A. COOK.

In an attempt to correlate the property of the blood which neutralizes the virus of herpes with the sex and particular physiologic state of the donor, the serums of 102 women and 66 men were tested by means of a previously standardized protection test in white mice. All of the women's serums were obtained from patients at the Chicago Lying-in Hospital and represented the residue from specimens sent to the Wassermann laboratory of the Billings Hospital. Forty-six of the serums from men were obtained from adult patients in the university clinics and 20 from apparently healthy adults.

The virus, HF strain, was neutralized by 89 of the 102 specimens from women (i. e., by 87 per cent) and by 54 of the 66 specimens from men (82 per cent). Therefore, no evidence of a significant sex difference in the distribution of herpetic antiviral substances in the blood was indicated.

An investigation of the clinical records of the various women contributing serum revealed that 48 samples were derived from women in various stages of pregnancy and 54 from patients with more or less mild gynecological ailments of too wide a variety to permit classification. Forty-six of the former specimens, or 95.8 per cent, and 43 of the latter, or 79.6 per cent, showed the antiviral property.

The data from the gynecological cases were then analyzed with a view to determining any relationship of the presence of the antiviral property in the serum to the particular stage of the menstrual cycle at which the specimen was drawn. Unfortunately, however, the distribution of the specimens through the various stages of the cycle was very uneven, the numbers in the premenstrual

(one to five days) and menstrual groups being too small for significance. While possibly a lower incidence of the virucidal property in the serums drawn during and after the bleeding phase is suggested, the evidence does not justify a conclusion.

A Congenital Aneurysm of the Membranous Part of the Interventricular Septum. Morris Lev.

Two hearts from Mongolian idiots aged 5 and 13 months, respectively, are presented, each with an aneurysm of the membranous portion of the interventricular septum. In case 1 the aneurysm involved the complete extent of the membranous part, while in case 2 only the anterior half formed the aneurysm. In both instances, the aneurysm extended into the upper third of the base of the medial leaflet of the tricuspid valve, bulging into the right auricle and right ventricle. The following additional abnormalities were present in both hearts: (1) an abnormal direction of the muscular interventricular septum toward the lumen of the aorta; (2) an obliquely situated pars membranacea; (3) a shortened anterior tricuspid ledge on the anterior wall of the right ventricle, and (4) a markedly patent foramen ovale with fenestrations of the septum primum. In addition, in case 2 there were a remnant of the conus of the "right" aorta and an abnormal coronary sinus and thebesian valve. Aside from a few verrucae on the medial and anterior leaflets of the tricuspid in case 1 no further evidence of inflammation was present in either heart.

Since Laënnec described his case in 1826, about 70 cases of aneurysm of the membranous part of the interventricular septum have been reported in the literature. Thurnam intimated but Reinhard first definitely suggested that such an abnormality might have a congenital origin. However, most of the earlier authors, including Pelvet in 1867, considered aneurysm of the pars membranacea the result of endocarditis in all cases. Legg in 1884 clearly showed that there is a purely congenital type, differentiating this from an assumed acute endocarditic variety. Mall in 1912 demonstrated the abnormal direction of the muscular septum and aorta in such cases and stated that an aneurysm of the membranous part of the septum is due to an insufficient shifting of the septum to the right and of the aorta to the left. He thus considered all such aneurysms congenital. Cannell in 1930 and Massig in 1934 confirmed the anatomic findings of Mall.

In an attempt to clarify the etiology of such aneurysms, the reports of 66 cases with the interpretations of the various authors were examined. The hypotheses which have been advanced are: 1. The anomaly is the result of endocarditis (with or without left ventricular hypertrophy). 2. It results from the pull of a thickened and shortened leaflet of the tricuspid valve, with increased left ventricular pressure. 3. It is caused by atherosclerosis. 4. It is a congenital malformation of the pars membranacea with or without left ventricular hypertrophy and with or without inflammation.

From my study, the only hypotheses deemed of sufficient importance to be considered in the etiology are: (1) that of a congenital malformation of the pars membranacea and (2) that of an inflammation of this part with or without left ventricular hypertrophy. Among the 66 cases studied, in 32 the condition was considered as definitely, in 12 as probably, and in 22 as possibly, congenital. It is uncertain that endocarditis alone can produce an aneurysm of the membranous part of the septum.

In the determination of the underlying embryologic fault in this anomaly the following theoretical possibilities may be considered: (1) persistence of the bulboventricular ridge; (2) abnormal formation of the endocardial cushions; (3) abnormal formation of the bulbar swellings, and (4) abnormal direction of the ventricular and aortic septums (Mall). Of these possibilities the theory of Mall is the one best substantiated by anatomic observation. Beside the cases of Cannell, Massig, Eakin and Abbott, Mall, MacCallum and Rokitansky, my two cases seem to offer further proof of the abnormal direction of the muscular septum in relation to the aorticopulmonary septum in this abnormality.

A slight amplification of Mall's theory may be considered. From a study of the muscle bundles of the right ventricle in these two hearts and the abnormal

position of the aorta, straddling the interventricular septum, aneurysm of the membranous part of the septum probably is a mild form of transposition or detortion. This is manifested by a displacement of the aorta which leads to an abnormal formation and oblique or horizontal situation of the membranous portion of the interventricular septum. The ensuing weakness in this region may result in the formation of an aneurysm. Whether the actual formation of the aneurysm occurs in utero is conjectural. When, as in the cases described here, the base of the leaflet of the tricuspid valve is displaced and the affected leaflet is atrophied, the aneurysm may be considered to have been formed in fetal life during the period when the valve structure is muscular (Goehring).

EMBOLIC PULMONARY LESIONS PRODUCED IN RABBITS BY HUMAN FAT CONTAINING FATTY ACIDS OR SOAPS OF CALCIUM, STRONTIUM OR BARIUM. EDWIN F. HIRSCH.

The complete report is published in this issue of the ARCHIVES, page 765.

"RETOTHEL SARCOMA" SIMULATING A TUMOR OF BONE. GEORGE LOFDAHL and VICTOR LEVINE.

A 23 year old white man noticed a tumor developing on the right ninth rib. This was removed, and the site was treated with roentgen rays and radium, but the growth recurred after nine months. Removal and radium treatment were followed by a second recurrence after nine months. The same treatment was followed by a third recurrence five months later. This time the tumor had spread so that two additional ribs were removed. After another five months a cutaneous nodule was found in the last operative scar. At the same time roentgen films disclosed metastases in the lungs. Shortly afterward a nodule appeared suddenly in the right scapula. Radium treatment caused its disappearance.

From then on the patient became rapidly worse, with pain in the legs and difficulty in walking and breathing. This was followed by a sudden onset of paralysis of the lower extremities. Three weeks later he died, at the age of 26. The clinical diagnosis on the basis of a microscopic examination of tumor nodules was sarcoma of bone at first and later Ewing's sarcoma.

At postmortem examination the missing ribs beneath the operative scars were replaced by a firm yellow tumor mass measuring 15 by 9 by 3 cm. Extensive metastasis was present in the diaphragm, liver, both lungs, the pulmonary hilus and the right axillary lymph nodes. Single metastatic areas were found over the right scapula, on the inside of the sternum, in the left kidney, in the stomach and in the jejunum. A plaque of metastatic tumor tissue was present in the epidural space of the midthoracic region of the spine, causing pressure destruction of the spinal cord. All the metastatic areas were soft, light yellow and medullary. They varied from 0.7 to 10 cm. in diameter. In addition, there was cysto-ureteropyelitis with ascending pyelonephritis.

At the first operation the primary tumor measured 8.5 by 6 by 4.5 cm. On reviewing the case it was decided that this tumor had arisen between the rib and the pleura and that it had compressed and destroyed the rib. The histologic structure was the same in all the specimens examined. The tumor masses were composed of a reticulum of large cells with light-staining round, oval or indented nuclei, which closely resembled reticular cells. Many cells in mitosis were present. With silver stains the fibrillar reticulum about the blood vessels stained black, but the cellular reticulum did not. The final diagnosis was reticular cell sarcoma arising between the right ninth rib and the pleura. Roulet has abbreviated the name of this type of neoplasm to "retothel sarcoma."

Retothel sarcoma is the most important tumor of the reticulo-endothelial system and may arise anywhere in the body, although it most often arises from lymphatic tissue. It is distinctly different from Ewing's sarcoma, which is an undifferentiated round cell sarcoma displaying no histologic reticular features. The sarcoma described here was similar to that which Ehrlich and Gerber called "the reticular form of lymphosarcoma."

Book Reviews

Die unsichtbaren Krankheitserreger filtrierbare Vira. Ein Lehrbuch für Aerzte und Tierärzte. By Dr. Josef Baló. Paper. Price, 24 marks. Pp. 311, with 42 illustrations (3 colored plates). Berlin: S. Karger, 1935.

Since the first recognition of a filtrable virus, in 1892, when it became known that the causative agent of mosaic disease of the tobacco leaf can pass through a filter which retains bacteria, a rich literature on filtrable viruses has accumulated. However, there have been published only three larger books and four fairly small reviews in monographic form. The first book on the subject, by Thomas M. Rivers, appeared in 1928 and was dedicated to the memory of Charles E. Simons. Baló received his training under Simons at the School of Hygiene of Johns Hopkins University and first wrote a book on filtrable viruses in Hungarian in 1931. For the present German edition the material was brought up to date and completely rewritten.

A general part, which fills 42 pages, takes up the size of the viruses, their cultivation and staining, their affinity for certain tissues, the protoplasmic reactions and nuclear inclusions, the mechanism of immune reactions during and after recovery from virus diseases, including complement fixation, precipitation, and agglutination, and the multiplicity of viruses and their interrelations as well as the relations between the viruses and the bacteria and between the viruses and the host.

The special part is divided into ten chapters. The first chapter deals with smallpox, postvaccinal encephalitis and various forms of animal pox. Then follow chapters on the different forms of herpes, neurotropic viruses, organotropic viruses and virus diseases which resemble septic infections. The sixth chapter is devoted to a discussion of the tumor-like conditions which are due to the action of viruses. The question of filtrable forms of bacteria and of protozoa, including the bacteriophage, is discussed in a separate chapter. The three final chapters deal with the lymphocystis disease of fishes, the diseases of caterpillars and bees and the mosaic diseases of plants. The final ten pages are given over to a discussion of the technic of filtration and of ultrafiltration.

The presentation of this difficult subject-matter is clear and satisfactorily complete. The treatment of the many controversial problems is objective and illuminating. The illustrations are excellent. According to the author the review of the literature includes the publications up to October 1934. However, in the chapter on measles the rather important results of the recent contributions to histopathology are not included. The bibliographic references are obviously incomplete, and in one chapter they reach only to the middle of the alphabet, apparently owing to an error in printing.

Delafield and Prudden's Text-Book of Pathology. Revised by Francis Carter Wood, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University. Sixteenth Edition. Price, $10. Pp. 1,406, with 861 illustrations. Baltimore: William Wood & Company, 1936.

Notices of the thirteenth and fifteenth editions of this textbook have appeared in the ARCHIVES (**1**:496, 1926, and **12**:686, 1931). The notice of the thirteenth edition contains a brief account of the history of the book.

In the preface to the present edition the reviser writes that many requests have been received "to render the book 'more modern,' but unfortunately modernity is largely only a changing of the labels on the specimen bottles. People still have the same lesions that they had when Delafield and Prudden wrote the first edition, even though the names may have been changed, and it is important for the student

to learn these lesions. It is not an easy book to read and it was not written to help the student practice medicine except in so far as it taught the fundamentals upon which medicine rests. At the time at which it was first published there was no sentimental attitude toward lightening the labors of the student who was supposed to work out matters largely for himself and get his practice of medicine from the professor of that subject. Nevertheless the editor has noticed that it is often used as a reference work by those long past their student days because of the vast amount of information which it contains and the numerous references to the literature of pathology. In the light of this situation no attempt has been made to introduce much of the modern experimental work in physiological and clinical lines, interesting as it may be. This whole field is in rapid flux and not without contradictions. Hence the volume has been left as much as possible as it was written by those two famous men who made so many contributions to pathological anatomy and histology. The book has already reached the limit for comfortable handling in attempting to cover even incompletely the subject with which it deals and any increase in size is therefore prohibited."

This statement indicates the limitations of the book as it now stands. It is weak in its accounts of the recent advances of pathology, but it gives a good presentation of the knowledge of pathology up to about ten years ago. The most extensive changes have been made in the chapter on nervous diseases, which has been revised thoroughly by Edwin M. Deery.

Vorkommen und Verbreitung der Thyreotoxicose in Schweden. Zur geographischen Pathologie des Morbus Basedowi und verwandter Krankheiten. By Thor Sällström. Pp. 206, with 52 illustrations. Stockholm: Klara Civiltryckeri A.-B., 1935.

This study is based on 5,450 cases of thyrotoxicosis in Sweden, 2,255 of the cases being in persons living in cities and 3,195, in persons living in the country. In about half of the cases the patients were living where the disease first showed itself. The statistical analysis of the cases indicates that thyrotoxicosis is limited to a definite geographic area in Sweden. The disease is relatively more frequent in cities than in the country, but the cities with the higher incidence of the disease lie in districts in which the total number of cases is also high. The distribution of the disease does not seem to be dependent on the density of the population. It tends to occur in industrial centers; farmers are not affected so frequently as persons working in the industries and the professions. The subjects studied included 4,950 women and 500 men, the ratio of women to men being 9.89 : 1. Taking the data as a whole, the maximum point of the curve for age lies between the years from 36 to 40. Thyrotoxicosis with nodular goiter is also limited to definite localities, but this distribution does not correspond with the prevalence of endemic goiter or thyrotoxicosis. A definite correlation between thyrotoxicosis and goiter does not seem to exist in Sweden. In certain large districts, thyrotoxicosis may be associated with endemic goiter, but in other and larger districts there is no agreement between the occurrence of thyrotoxicosis and goiter. Secondary thyrotoxicosis is more frequent in districts in which goiter is common, but the incidence of goiter is not greater in patients with thyrotoxicosis than the general incidence of goiter in the same region. It is true, however, that in families in which thyrotoxicosis occurs there is a higher incidence of goiter than in the general population. It appears from these observations that thyrotoxicosis is more prevalent in areas with a continental climate than in those with a maritime climate; several facts point to the climate as significant in determining the distribution of thyrotoxicosis.

Le fonctionnment du rein malade. Diurèse, albuminurie, oedème, glycosurie, classification des néphropathies, recherches expérimentales et cliniques. By Paul Govaerts. Paper. Price, 25 francs. Pp. 214. Paris: Masson & Cie, 1936.

This monograph contains an exceptionally unbiased and brief presentation of the various theories of the mechanism of renal secretion and a description of

the pathogenesis of the major phenomena of nephritis. In discussing the mechanisms of urine formation Govaerts includes both sides of the long and often bitter controversy between the exponents of the secretion-reabsorption theory and those who include tubular secretion as one of the processes in the elaboration of the urine. The investigations of Heindenhain, Volhard, Lamy, Mayer, Rathery and others are mentioned, as well as the theories of Ludwig, Cushny, Rehberg, Starling and Richards. The author's conclusion that both processes are involved is lucid, concise and rational; it conforms with the opinions of the best American students of this complex and confusing problem.

Following the discussion of the mechanism of the secretion of urine are excellent chapters on diuresis, albuminuria, edema, hypertension secondary to nephropathy, the Rehberg clearance studies, renal glycosuria and a classification of nephritis. Weakest among these discussions is that dealing with the circulatory disturbances, such as arterial hypertension, which is seen associated with nephritis. The classification presented is but slightly and insignificantly different from that of Volhard and Fahr.

The book is well printed with large, clear type but is poorly bound; the paper cover became detached in a few minutes of handling. The bibliography is international, modern and well chosen. The American medical literature is better represented than is usual in Continental works. To those with particular interest in renal disease this volume will serve to present the modern French attitude.

Medical Mycology. Fungous Diseases of Men and Other Mammals. By Carroll William Dodge, Ph.D., Mycologist, Missouri Botanical Garden; Professor, Henry Shaw School of Botany, Washington University, St. Louis. Price, $10. Pp. 900, with 142 illustrations. St. Louis: C. V. Mosby Company, 1935.

This book grew out of Dodge's course on medical mycology, which was begun at Harvard University in 1924. It is the result of at least ten years of preparation. The first seven chapters are devoted to general mycology. Here are presented clearly and competently, with appropriate references, the morphologic and physiologic features of fungi, their artificial cultivation, isolation, microscopic examination and nomenclature. The international rules of botanical nomenclature, on which the classification of fungi is based, are explained fully. The rest of the book, about seven hundred and seventy pages, gives a systematic consideration of the fungi regarded as pathogenic for man or other mammals. The guiding principle is the botanical classification and naming of the fungi as determined by an exhaustive review of the vast literature on the various aspects of fungous diseases and the author's own work. The thoroughness of the author's study of the more strictly medical part of the literature is remarkable. Special efforts have been made to secure complete bibliographies (to the end of 1933) and to avoid errors. The bibliography of Endomycetales, for instance, covers no less than fifty pages. The book contains an enormous amount of properly arranged, scholarly, accurate, well illustrated and completely indexed information about pathogenic fungi. In its field it is unquestionably the foremost book in the English language, and it will be welcomed warmly by students of the fungous mammalian diseases everywhere.

Le thymus: Anatomie — histologie — physiologie — clinique et thérapeutique. By G. Worms, Médecin-Colonel, Professeur du Val-de-Grâce, and H. Pierre Klotz, Interne des hôpitaux de Paris. Price, 30 francs. Pp. 152, with 65 illustrations. Paris: Masson & Cie, 1936.

This monograph is based mainly on the newer French literature on the thymus. There are five chapters, on the following aspects of the thymus: embryology and general morphology, normal and pathologic histology, physiology, pathology and treatment. Many of the illustrations are difficult to understand because the drawing is crude. The essential element of the thymus is the small cell, the

thymocyte, in the cortex. The thymocyte is of epithelial origin, and as it is rich in nuclein it may play a rôle in the distribution of nuclein according to the needs of growth, in which the thymus seems to be one of the essential regulatory factors. Hassall's bodies are regarded as epithelial and mesoblastic formations closely associated with the local disintegration of the thymocytes. The review of the clinical and roentgenologic observations in cases of hyperplasia of the thymus as a cause of sudden death leads to the conclusion that authentic cases of this condition must be extremely rare and difficult to diagnose. The discussion of status thymicolymphaticus ends as follows: "If it appears difficult to deny the existence in nurslings of a special state predisposing to sudden death, the role and even the existence of thymic hypertrophy in this constitution appear most problematic." The book gives a good review of the knowledge of the thymus, especially as represented in the French literature.

Biologische Untersuchungen über Farbstoffe. Volumes I and II. By Iwao Matsuo, Professor der Medizin der Kaiserlichen Universität zu Kyoto. Cloth. Pp. 1,043. Kyoto, 1935.

These two large volumes, comprising more than 1,000 pages, summarize the results and conclusions derived from a systematic study of the physical and chemical properties of dyestuffs and their absorption and excretion by animal tissues. The work covers a ten year period and includes the observations of the writer, his colleagues and forty-six students, on more than 300 different dyes.

Beginning with the properties of the dyestuffs themselves, the studies are concerned with the absorption of these substances by almost every organ and tissue of the body and their excretion by every possible route, including the various serous cavities. The liver and kidneys naturally are accorded a great deal of attention as the chief organs of excretion. The physiologic data thus obtained are applied to the development and interpretation of function tests. However, the excretion of dyestuffs by other organs and into the serous cavities is also of practical interest because of the employment of certain dyes having antiseptic properties.

These volumes contain a wealth of information relative to the subject matter. Some of the material presented is of direct clinical interest, but most of it will have greater appeal to the physiologist and clinical investigator. Unfortunately, the lack of a subject index will limit their usefulness as reference books.

Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher. From His Present and Past Associates and House Officers at the Peter Bent Brigham Hospital, Boston, Mass. In Honor of His Sixtieth Birthday, February 17, 1936. Cloth. Price, $10. Pp. 1,000 with illustrations. Baltimore: Waverly Press, Inc., 1936.

At the clinicopathologic conference in the Peter Bent Brigham Hospital in Boston, on Feb. 17, 1936, this volume was presented to Henry A. Christian in honor of his sixtieth birthday. The book contains more than one hundred articles on various topics of current interest in the field of internal medicine by associates of the dedicatee in the Peter Bent Brigham Hospital. At the end of the book is a register of the former and present members of the medical staff of the hospital—two hundred and ninety-one in all. The introduction and "an appreciation" present a good account of the training, labor and achievements of Dr. Christian. The book is an impressive record of his results in developing and conducting a great medical clinic.

Books Received

MANUEL DE BIOCHIMIE. Pierre Thomas, de l'Institut Pasteur, Professeur de Chimie biologique à la Faculté de médecine de Cluj. Price, 180 francs. Pp. 978, with 52 illustrations. Paris: Masson & Cie, 1936.

CARDIAC OUTPUT AND ARTERIAL HYPERTENSION. Sidney A. Gladstone, M.D. Price, $1. Pp. 56, with 4 illustrations. New York: The Author, 1935.

CANCER COMMISSION COMMITTEE STUDIES OF THE CALIFORNIA MEDICAL ASSOCIATION. Price, 75 cents. Pp. 129. San Francisco: J. W. Stacey, Inc., 1936.

PARENTERAL THERAPY. A READY REFERENCE MANUAL OF EXTRA-ORAL MEDICATION FOR PHYSICIANS, DENTISTS, PHARMACISTS, CHEMISTS, BIOLOGISTS, NURSES, MEDICAL STUDENTS AND VETERINARIANS. Walton Forest Dutton, M.D., and George Burt Lake, M.D. Cloth. Price, $7.50. Pp. 376, with 90 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1936.

DER ENDEMISCHE KRETINISMUS. Prof. Dr. F. de Quervain, Vorsteher der chirurgischen Universitätsklinik Bern, and Prof. Dr. C. Wegelin, Direktor des pathologisch-anatomischen Instituts der Universität Bern. Paper. Price, 24 marks. Pp. 206, with 120 illustrations. Berlin: Julius Springer, 1936.

THE FIFTY-FIRST ANNUAL MEDICAL REPORT OF THE TRUDEAU SANATORIUM AND THE THIRTY-FIRST MEDICAL SUPPLEMENT FOR THE YEAR ENDING SEPTEMBER 30, 1935, TOGETHER WITH THE NINETEENTH COLLECTION OF THE STUDIES OF THE EDWARD L. TRUDEAU FOUNDATION FOR RESEARCH AND TEACHING IN TUBERCULOSIS, 1935.

THE SARANAC LABORATORY FOR THE STUDY OF TUBERCULOSIS OF THE EDWARD L. TRUDEAU FOUNDATION. REPORT OF THE DIRECTOR AND FINANCIAL REPORT FOR THE YEAR ENDING SEPTEMBER 30, 1935. REPRINTS OF SCIENTIFIC PAPERS. Saranac Lake, N. Y.: The Saranac Lake Academy of Medicine, 1935.

THE HARVEY LECTURES. Delivered under the auspices of the Harvey Society of New York, 1934-1935, under the patronage of the New York Academy of Medicine. Dr. W. Bosworth Castle, Dr. William Cumming Rose, Dr. Wilbur A. Sawyer, Dr. Alfred N. Richards, Dr. E. C. Dodds, Dr. G. V. Anrep, Dr. Francis G. Blake and Dr. John H. Northrop. Series XXX. Cloth. Price, $4. Pp. 270, with illustrations. Baltimore: Williams & Wilkins Company, 1936.

THE ADRENALS. Arthur Grollman, Ph.D., Associate Professor of Pharmacology and Experimental Therapeutics and formerly Associate Professor of Physiology, in the Medical School of the Johns Hopkins University. Cloth. Price, $5. Pp. 410, with 17 illustrations. Baltimore: Williams & Wilkins Company, 1936.

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